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FOR THE YEAR BEGINNING JULY 1, 1974,
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(FISCAL YEAR 1975)

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LETTER OF TRANSMITTAL

VETERANS' ADMINISTRATION,
Washington, D.C., April 15, 1976.

Hon. RAY ROBERTS,
Chairman, Committee on Veterans' Affairs, House of Representatives,
Washington, D.C.

DEAR MR. CHAIRMAN: I am pleased to send you this 20th Annual Report of Medical Research in the Veterans' Administration for the fiscal year 1975. Thanks to your committee's support we may present it as a way station on a continuous journey of discovery through two decades of scientific endeavor oriented to improve the quality of health care delivered to our veterans in almost every medical discipline. The general acceptance of the improved clinical practices resulting from VA medical research not only pays tribute to the soundness of the research but, more importantly, delivers better health care to persons of all ages everywhere.

Sincerely,

RICHARD L. ROUDEBUSH, *Administrator.*

FOREWORD

During fiscal year 1975, medical research in the Veterans Administration continued its attack on humanity's greatest killers as well as on the multiplicity of injuries and illnesses that plague our veterans and the community at large.

Supported by state and local heart associations, a Long Beach, Calif. VA cardiologist and his colleagues directed the screening of 2,524 Long Beach citizens with no history of heart disease. They evaluated six major risk factors known to predispose people to coronary heart disease. Results were given to subjects and their physicians, with briefings of those considered to be serious risks. The study showed that the best approach to the epidemic of coronary heart disease is prevention; first, by detecting the presence of risk factors, then beginning long-term treatment.

The VA Cooperative Study Group on Antihypertensive Agents—largely responsible for world-wide efforts to discover and treat high blood pressure—found that a small number of older persons with initial records near the lower limit of high blood pressure, after two years or more of medical management which put them within the normal range, may remain normal indefinitely, even if medication is stopped.

Radioimmunoassay—a discovery of the Solomon A. Berson Research Laboratory, Bronx VA Hospital, New York City—made possible the further discovery by investigators at the Berson Laboratory and in the Pulmonary Disease Section, VA Hospital, East Orange, N.J., that lung cancer tumor cells produce "Big ACTH," and adrenocorticotrophic hormone of giant molecules compared to the same hormone produced by the pituitary gland. When the primary site of the tumor is unknown, the probability of the site being in the lung is favored if "Big ACTH" can be detected in the tissue. Now the disease may be found early enough for successful treatment in many cases, and the new discovery may also be used to evaluate the success of the treatment. Lung cancer is the most common cancer among males.

A San Francisco VA Hospital research biologist, studying cell-walls of normal and cancerous human breast tissue with the scanning electron microscope, made a breakthrough in the diagnosis of breast cancer. She found that certain cells lining ducts in normal breast tissue were covered with microvilli (tiny hair-like projections) that gave them a brush-like appearance when magnified up to 10,000 times. In cancerous tissue, however, the microvilli were enlarged and clumped together and exhibited other irregularities making the cancer tissue identifiable at a glance.

A microbiologist at the VA Hospital, Salt Lake City, Utah demonstrated how macrophages—large scavenger cells of the immune sys-

tem—may be activated by immunological agents, such as bacillus Calmette Guerin (BCG), a tuberculosis vaccine, so that a change occurs—perhaps in their cell-walls—and the macrophages destroy cancer cells in a test tube culture.

The Normative Aging Study at the Boston VA Outpatient Clinic gives encouragement to the aging. Indications are that adaptation to aging, and even the aging process itself, unlike disease or injury, is to some degree under the control of the individual. Choices of diet, exercise, habits of drinking and smoking, and life-style may lend an advantage to coping with advancing age. In optimal health care for the aging, the study suggests that a gerontologist should include counseling and education calculated to involve the individual in beneficial activity as well as any necessary treatment for disease or injury.

Investigators at the Bronx VA Hospital, New York City found that large doses of vitamin C may destroy 50 to 95 percent of the vitamin B_{12} contained in a meal. Vitamin B_{12} is the most potent defense known against pernicious anemia. Concerned about pain following chest surgery, which prevents patients from coughing and breathing deeply enough to avoid pulmonary complications, surgeons at the VA Hospital, Albuquerque, New Mex. froze nerves between the ribs, permitting a painless convalescence with a return to normal sensation after about six months.

The VA Prosthetics Center in New York City has developed a number of myoelectrically controlled hooks, capable of unusually high grasping force to supplant amputated hands. The Center also has tested prototypes of a unique combination power-bed and wheelchair. These permit a helpless patient without the use of arms or legs to have independent mobility within a hospital or around a ranch-style home and patio. The Center has designed and made ambulators which permit a patient, who cannot stand independently, to work in the upright position and move voluntarily for short distances on level surfaces. These devices also allow activity in narrow spaces which do not admit a wheelchair.

VA investigators have made progress in preventing the type of blood vessel disease that causes the loss of limbs. They have had increasing success, when surgery is necessary, in operating below the knee and often at the ankle, in contrast to the older amputations of the entire leg. Immediate post-surgical prosthetics management results in quicker rehabilitation and discharge of patients, and the cost of an artificial foot is substantially below the cost of an artificial leg.

VA medical research continues to be productive in providing new knowledge helpful to veterans and other individuals in meeting their health needs. It provides an irreplaceable support to the medical care of veterans in that it assists in the recruitment of outstanding clinicians and finally, it demonstrates the merit of pursuing the answers to relevant questions in a setting that provides the capability for the rapid application of these advancements to the individual patient. It continues to be recognized by the world scientific community as evidenced in the Honors and Awards Section of this report.

John D. Chase, M.D.,
Chief Medical Director.

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MEDICAL RESEARCH IN THE VETERANS' ADMINISTRATION

HIGHLIGHTS OF VA RESEARCH ACCOMPLISHMENTS FISCAL YEAR 1975

Introduction

During the past fiscal year, continued progress in medical research has produced important findings which are discussed briefly below. The scientific developments, as presented here, are selections which form a composite of additions to the field of medical knowledge which provides hopeful clues to solutions of single ailments and groups of disorders. All the accomplishments noted in this section have appeared as published research papers or have been presented at scientific and professional meetings.

It should not be assumed, however, that various studies mentioned in these highlights are of greater significance, specifically, than others which may not have been cited.

Effective prognosis for survival of prostatic cancer patients

To predict the survival of patients with prostatic cancer, physicians have relied heavily on the clinical stage of the disease when the patient arrives for treatment as well as the pattern revealed by the microscopic study of cell structure of the tissue involved. In addition, a normal electrocardiogram and no history of cardiovascular disease have been favorable indications. Otherwise, means for prognosis in these cases has been limited.

Recently, the VA Cooperative Urologic Research Group reported on an additional aid for predicting survival of these patients. The study involved 750 patients in hospital and outpatient clinics at 21 VA facilities. Nonprotein-bound serum cortisol (NPC), and total 17-hydroxycorticosteroid (17-OHCS) levels were determined before and after treatment. In general, it was found that the lower the initial value of NPC and 17-OHCS, the greater the probability of survival during the first year of treatment. The levels of these steroids appeared to be a better prognostic indicator of survival in the first year than did the patient's age, treatment, or stage of the disease.

Change in blood pressure after stopping treatment

Studies by the VA Cooperative Study Group on Antihypertensive Agents have indicated that adequate control of blood pressure for a sustained period on medication could result in a permanent modification in a small number of cases.

A group of 86 male patients with established hypertension had been treated for two years or longer with an effectiveness indicated by an average diastolic pressure below 96 mm. Hg during the last year of treatment. Older persons and those whose blood pressures were at the lower end of the spectrum of "high" blood pressure at the time medication started were most apt to remain with normal pressure after treatment stopped.

Advances in lung cancer detection

Investigators from the Pulmonary Disease Section, VA Hospital, East Orange, N.J. and the Solomon A. Berson Research Laboratory, VA Hospital, Bronx, N.Y., report that the production of adrenocorticotropic hormone (ACTH)—in a "Big" form molecularly larger than the pituitary ACTH—in lung tumors is clincially useful as a biological marker in lung cancer. "Big ACTH" has no bioactivity and leads to no clinically detectable endocrine syndromes, such as Cushing's disease.

The immunossay of "Big ACTH" is potentially useful in both diagnosis and treatment of lung cancer—the most common cancer in males. Because of the great sensitivity of radioimmunoassay, surgery may be unnecessary to obtain diagnostic specimens. In this study, bronchial washings also contain "Big ACTH."

The report further suggests that in cases in which lymph node or liver biopsy specimens are histologically positive for cancer, but the primary site of the tumor is unknown, the probability of the site being in the lung is favored if "Big ACTH" can be detected in the tissue.

Breakthrough in diagnosis of breast cancer

During a study of plasma membranes of cells from normal, cancerous, and other abnormal human breast tissue, a San Francisco VA research biologist discovered alterations in the appearance of the plasma membrane of glandular epithelial cells lining the mammary ducts. Specimens of cancerous breasts (even from the supposedly normal portions), or noncancerous abnormal breasts, could be distinguished from normal.

Normal epithelial cells have a plasma membrane that appears to have a multitude of minute, hair-like projections, known as microvilli, giving the cells the appearance of brushes. Specimens from cancerous tissue show three distinct alterations of the microvilli, by which the investigators could easily distinguish the specimens of cancerous breast tissue from all other specimens.

Coronary-risk screening

In an attempt to arrest the development of the current high mortality in coronary heart disease, a VA cardiologist and colleagues began a long-term epidemiologic study sponsored by the Long Beach, California Heart Association. They screened 2,524 Long Beach citizens, mostly in their forties and fifties, with no history of heart disease. Six major risk factors known to predispose people to coronary heart disease were evaluated.

The investigators found that in many adults showing no symptoms, risk factors predisposing to coronary heart disease are not being detected or treated. They conclude that the best approach to the epidemic of coronary heart disease is prevention; first, by detecting the presence of risk factors and then, by starting long-term treatment.

Electrocardiogram analysis by computer

From the VA Hospital, Washington, D.C., computer analyses of electrocardiograms (ECG's) were submitted to a diagnostic test against two of the nation's expert cardiologists. The result was cardiologists 64 percent correct, computer 88 percent correct.

The computer has a precise memory of the profiles of many thousands of patients with known heart diseases. If a new record resembles a profile in the computer's memory, a diagnosis can be made.

Independently, cardiologists at the VA Hospital, Minneapolis, Minn., tested the computer analyses in more than 1,000 cases and found it 88 percent correct, a degree of reliability they judge sufficient to warrant using the computer for ECG analysis on a routine basis.

Pain following chest surgery alleviated by nerve-freezing

Pain after chest surgery limits the ability of patients to breathe deeply and cough frequently enough to avoid pulmonary complications. Drugs given to relieve the pain often leave the patient with shallow respiration and inadequate coughing reflex.

To overcome these difficulties, a new technique called "cryoneurolysis" was carried out on 38 patients, with an equal number of controls, at two hospitals—the VA Hospital, Albuquerque, N.M. and the Roswell Park Memorial Institute.

A significant decrease was found in the need for narcotic dosage during the postoperative period when cryoneurolysis was used. This process anesthetizes the incision and does not require repetition. The patients breathe deeply and cough normally during convalescence and are easily able to sit up and use the arm on the operated side, which greatly simplifies nursing care.

National study of operating room hazards

An investigator at the VA Hospital, Ann Arbor, Mich., was largely responsible for a national study by the American Society of Anesthesiologists (ASA) identifying risks to some hospital personnel. It found that breathing waste anesthetic gases in the operating room (OR) is hazardous to health and that OR personnel had a significantly higher incidence or cancer, kidney and liver disease, and abortion. Also, there was a far greater incidence of birth defects occurring among children of these health professionals than among professional people not working in operating rooms.

The hazard, first noticed in Russia and European countries, was confirmed in the U.S. by studies of Michigan OR personnel by the VA investigator who brought it to the attention of the ASA. His preliminary findings strongly suggest that the anesthetic gases are at least partly responsible for these hazards—particularly birth defects and

cancer. Several anesthetic gases are similar in chemical structure to known human carcinogens. The investigator strongly recommends venting waste anesthetic gases at all locations where anesthetics are given.

Drug dependence research

Exploring the possibility that different classes of psychoactive drugs exert different patterns of effects on sleep, medical investigators at the VA Hospital, San Francisco, Calif., studies the effects of a high dosage of tetrahydrocannabinol (THC)—considered to be the main ingredient of marijuana—on the sleep patterns of young patients, average age 25 years, who were accustomed to using marijuana.

In the present study, administration and withdrawal of high dosages of THC induced striking changes in electroencephalogram (EEG) sleep patterns. These effects were far greater than those produced on waking EEG activity.

The investigators suggest that THC, because of its apparently unique pattern of effects on sleep, could prove to be a useful tool in understanding the mechanisms and pharmacology of sleep.

Infection surveillance reduces hazard in new hospital

Monitoring of hospital-acquired infection at the VA Hospital, Hines, Ill., led to the discovery of a near double increase of infections caused by bacteria in the blood of patients a few years ago. The finding was remarkable since it followed the relocation of patients to a new, 16-story hospital with all modern facilities.

The epidemic was found to be caused by *Pseudomonas aeruginosa* and a number airborne fecal flora—organisms commonly encountered in the human alimentary tract and in sewage. Through scientific tests, including air sampling, the source was traced to a chute-hydropulping waste disposal system interlinking all 16 floors of the new building, which contaminated the air. When the faulty disposal system was closed and sealed off, and a new method of disposal introduced, the number of airborne infective agents returned to normal. The report urges hospital designers to prevent the described sources of gross contamination and serious hazards to the hospital environment.

Pancreatitis treatment

Aside from different treatment for the two kinds of pancreatitis—hemorrhagic and edematous—the outlook is grave for the hemorrhagic form which has a mortality rate of 30–50 percent or higher, compared to a mortality of 5–13 percent observed in cases of edematous pancreatitis. Thus, early determination whether a patient has acute, swollen pancreatitis or the more critical hemorrhagic form is crucial to both treatment and prediction of the probable course and outcome of the disease.

Medical investigators at the VA Hospital, Sepulveda, Calif., report that the detection of methemalbumin in the blood serum or effusion from the abdominal or chest cavities of patients is virtually a certain indication of the hemorrhagic form of pancreatitis. They were able to make the crucial determination of the presence or absence of me-

themalbumin by means of a simple, quick spectrophotometric assay developed and reported by them earlier.

Diabetes treatment

Traditionally, the metabolic disorders of diabetes mellitus have been ascribed entirely to insulin deficiency. However, more recently, a research team at the VA Hospital, Dallas, Texas, has demonstrated two new lines of evidence supporting the theory that the opposing hormone, glucagon, is involved in the development of the severely high blood sugar levels that are typical of diabetes.

The research group found that development of this abnormally high blood sugar level does indeed require the presence of glucagon. Finally, suppression of glucagon in animals with experimentally induced diabetes led to a rapid reduction of the high blood sugar level. This suggests a potentially valuable new approach to the treatment of diabetes.

Danger of high doses of vitamin C

In the course of treating nine Vietnam veterans at the VA Hospital, Bronx, N.Y., who were receiving ascorbic acid tablets (vitamin C) to maintain a urine acid level sufficient to help prevent infection, investigators observed that four of the nine paraplegics had very low levels of serum vitamin B_{12}—the antianemia factor of liver extract and the most potent antipernicious anemia substance known.

Evaluating the reasons for this deficiency, the Bronx investigators discovered that large doses of vitamin C, such as those recently recommended for prevention of the common cold, may destroy from 50 to 95 percent of the vitamin B_{12} contained in a meal.

Research in nuclear medicine

Medical investigators at the VA Hospital, Lexington, Ky., have reported a new technique for the thyroid function test using the radioisotope ^{99m} Technetium-pertechnetate, which saves time and money while reducing the hazard of radiation exposure to the patient's thyroid gland by almost 10,000 times.

The results of their technetium thyroid-scan study were so nearly identical to the standard ^{131}I-radioactive iodine uptake (RAIU) test, that the investigators recommended that their new radioisotope technique be used in place of the 24-hour RAIU test in screening and diagnosing possible thyroid disease in the interest of saving time, money and radiation exposure.

Research in speech pathology

Speech pathologists have divided oral communication into two kinds—transmission of meaning and of emotion. The former relates to putting words together to convey an idea; the latter, to altering inflections or pitch of the voice to convey emotion. Not only a person's ability to convey information orally, but his ability to understand persons speaking to him may be disturbed by damage to the brain, such as in aphasia resulting from a stroke. Aphasic patients who are unable to use speech to convey ideas have been found to be able to

recognize the emotion conveyed by a voice even though they do not understand the words.

Investigators at the VA Hospital, Gainesville, Fla., recognizing an indication that the two kinds of speech comprehension are controlled by different areas of the brain, designed an experiment to determine if there are differences between the sides of the brain in the comprehension of the emotional content of speech.

The results suggest that aphasic patients with right-sided damage have a defect in comprehension of the emotional content of speech—medically referred to as auditory affective agnosia.

A new technique in oral biology

A medical investigator at the VA Hospital, West Haven, Conn., has made use of Scialom pins for setting fractures of facial bones which cannot be managed by splints. The pins bear the name of the French dentist who designed them originally for securing dental crowns. They are made of tantalum, a noncorrosive material used in transplantations, and range from one to two inches long and are similar to a hypodermic needle in diameter.

A single pin is relatively easy to insert into the bone surrounding the tooth socket. Since it does not adhere to the bone, but actually becomes loose in a short time, the pin can be withdrawn easily by the dentist after a few days. When the investigators fused together a double tripod of pins with three prongs extending into the lower jawbone and the opposite three embedded in the crown, the tri-plant was almost impossible to dislodge. The successful use of this procedure with animals and clinical results with four accident victims was reported this past year.

CONFERENCE ON VA STUDIES IN MENTAL HEALTH AND BEHAVIORAL SCIENCES

More than 600 registrants attended the 20th Annual Conference on VA Studies in Mental Health and Behavioral Sciences, April 9–11, in Chicago, Ill. One of the main features of the program was an invited address by Marat Vartanian, Chief of the Laboratory of Pathophysiology at the Institute of Psychiatry of the Academy of Medical Sciences in the Soviet Union, Moscow, who discussed biological studies of endogenous psychoses in the Soviet Union.

The keynote address was delivered by Dr. Neal Miller of The Rockefeller University, New York, on applications of learning and biofeedback to medicine and psychiatry. Reports on the current status of six VA Cooperative Studies included research on methadone, drugs and sleep, and recovery from aphasia. In addition to several symposiums concerning drug abuse, sexuality, mental health care and therapeutic developments, 12 teaching seminars were held in areas ranging from prescribing psychotherapeutic drugs, death and dying, to evaluative studies in treatment and prevention of suicide.

VA PARTICIPATES IN PSYCHIATRIC MEETING

One of the highlights of the 128th Annual Meeting of the American Psychiatric Association, Anaheim, Calif., May 5–9, was an all-VA

panel on "A View of Psychiatry in Moscow and Leningrad." More than 25 VA physicians and researchers either presented scientific papers, contributed to panel discussions, were moderators and/or presided as chairman of scientific sessions. Of particular note was a session on lithium in depression; a paper on treatment-related factors in alcoholic populations; and a session on drugs of abuse in which VA presented findings in research on EEG Sleep Patterns and Drug Abuse.

Walter E. Barton, M.D., VA Hospital White River Junction, Vt., and former Medical Director of the APA, receive the Distinguished Service Award. The Bronze Medal was awarded for a VA exhibit on "A Computer-Assisted Psychiatric Assessment Unit," and a scientific paper was presented describing this innovative approach to psychiatric decision-making.

SEVERAL VA SYMPOSIUMS HIGHLIGHT PSYCHOLOGICAL MEETING

One of the highlights of the 82nd Annual Meeting of the American Psychological Association, New Orleans, August 30–September 3, was a symposium sponsored by VA and the Division of Psychologists in Public Service, on "Coming of Age in the Delivery of Mental Health Services."

An all-VA symposium focused on "Impact on Patients of Transitions in Health Services" and a number of other symposiums, round table discussions, workshops and invited panels in which VA psychologists participated included such areas as: problems of older people; the aging woman; new directions in treatment and rehabilitation of head injury; cardiac considerations in rehabilitation; recent approaches to brain-language relationships; biofeedback phenomena; psychological functions in epilepsy research; treatment and research with drug users; and studies of brain-damage and schizophrenia. A VA exhibit presented the variety of professions necessary to maintain the VA hospital system. It contained an invitation to clinical and counseling psychologists and career professionals.

VA SPONSORS MEDICAL RESEARCH MEETING

To ensure a better understanding of the responsibilities of Medical Research Advisory Groups and their relation to each other, a combined meeting of these groups and Central Office personnel was held June 3–4, at the Sheraton National Hotel, Arlington, Va. This meeting, the first of its kind, was attended by members of the Program Research Advisory Group (PRAG), the Regional Research Advisory Groups (RAG), the Research Advisory Committee (RAC), and a number of Research Program Specialists.

The agenda included presentations by the Assistant Chief Medical Director for Research and Development; the Director, Medical Research Service; other VACO staff and selected Research Program Specialists who described the state of VA research in their specialty areas. In addition, two panel discussions were held; one on the Regional Research Advisory Groups, the other on the activities of the Research Program Specialists.

NATIONAL AND INTERNATIONAL AWARDS

During the fiscal year, four VA researchers received recognition on a national or international scale: Dr. Ludwik Gross, VA Hospital, Bronx, N.Y.; Dr. Roger Unger, VA Hospital, Dallas, Texas; Dr. Hubert Pipberger, VA Hospital, Washington, D.C.; and Dr. William Oldendorf, VA Hospital (Brentwood), Los Angeles, California.

The Albert Lasker Basic Medical Research Award was presented to Dr. Gross for his discovery that viruses induce, or cause, leukemia and cancer in mammals and for his continuing work in the biology and epidemiology of these viruses. His work stood alone for many years, yet today it is the basis of the major thrust in cancer research funded by the National Cancer Institute.

Dr. Unger's work has been recognized not once but twice. He received the Banting Medal of the American Diabetes Association and the David Rumbough, Jr. Award of the Juvenile Diabetes Foundation. The research which prompted these awards has shown that the body's blood sugar balance is maintained by two hormones—insulin, with a role which has been known for years, and glucagons, whose exactly opposite role was not appreciated. Dr. Unger's work is revolutionizing the understanding of diabetes and may lead to drastic changes in its treatment.

Dr. Pipberger pioneered in the computer interpretation of electrocardiograms—heart tracings. His very sophisticated technique is already used in examining patients. For his work, he received the Einthoven Medal from the University of Leiden, Holland.

Dr. Oldendorf received the first Ziedes des Plantes Medal from the Medical Physics Society of Würzberg, West Germany. Although he is a neurologist, Dr. Oldendorf originated an X-ray technique for scanning the brain. Called "transmission section" scanning, his concept is the basis for current computerized methods used for diagnosis.

WILLIAM S. MIDDLETON AWARD

The 1974 William S. Middleton Award, VA's highest honor for medical research, was presented to Paul A. Srere, Ph. D., Chief of the Preclinical Science Unit, VA Hospital, Dallas, Texas, and Professor of Biochemistry, University of Texas Southwestern Medical School. Dr. Srere was recognized for his outstanding accomplishments over the past 26 years and, particularly, for his research in the areas of protein chemistry, enzymology and cell biology conducted at the Dallas VA Hospital during the past 8 years. These included notable biochemical discoveries in key cellular metabolic pathways regulating lipid and carbohydrate synthesis and storage.

The award, named for the late Dr. William S. Middleton, famous clinician, educator, and VA Chief Medical Director from 1955–63, has been given each year since its inception in 1960. Dr. Middleton died September 9, 1975.

The first of these awards was given to the late Solomon A. Berson, M.D., Chief, Radiosotope Service and Senior Medical Investigator, and Rosalyn Yalow, Ph. D., Chief, Nuclear Medicine Service and Senior Medical Investigator at the Bronx VA Hospital, New York

City. They developed the technique of radioimmunoassay, an invaluable tool for detecting and measuring tiny amounts of biological substances. This has revolutionized the science of endocrinology. Since then the recipients have been:

1961: Hubert A. Pipberger, M.D., Chief, VA Research Center for Cardiovascular Data Processing, Washington, D.C. VA Hospital, who pioneered in computer interpretation of electrocardiograms.

1962: Leslie Zieve, M.D. and William C. Vogel, Biochemist, Minneapolis VA Hospital, for studies of phospholipids, and phospholipases.

1963: Stanley Ulick, M.D., Bronx VA Hospital, for his discoveries in the chemistry and metabolism of mineral corticoid hormones.

1964: Robert O. Becker, M.D., Chief, Orthopedic Section, Syracuse VA Hospital, for demonstrating that an electrical control system can be used to stimulate the regeneration of tissue in mammals.

1965: Lucien B. Guze, M.D. and George M. Kalmanson, M.D., Los Angeles VA Center, for discerning the host-parasite relationship in chronic, infectious kidney disease.

1966: Leo A. Hollister, M.D., Palo Alto VA Hospital, for numerous significant contributions in the field of therapeutic drugs for mental illness.

1967: Leonard T. Skeggs, Ph.D., Biochemist, Cleveland VA Hospital, for automated laboratory test devices and biochemistry of hypertension.

1968: Thomas E. Starzl, M.D., Chief, Surgical Service, Denver VA Hosiptal, for pioneering surgical transplantations of kidneys and livers, and the development of antilymphocyte globulin and other immunosuppressants to suppress the rejection of transplanted organs.

1969: Roger H. Unger, M.D., Associate Chief of Staff, Dallas VA Hospital, for his conception of the physiology of metabolism of fats and carbohydrates, basic to better therapy for diabetes patients.

1970: Andrew V. Schally, Ph.D., Chief, Endocrine and Polypeptide Laboratories, VA Hospital, New Orleans, La., for his investigations of the physiology and biochemistry of hypothalamic neurohormones.

1971: Marcus A. Rothschild, M.D., Chief, Nuclear Medicine, VA Hospital, New York City, for research in liver disease control mechanisms affecting serum albumin, and the pathophysiologic regulation of liver metabolism.

1972: Kenneth Sterling, M.D., Chief of the Protein Research Laboratory VA Hospital, Bronx, N.Y., for his outstanding accomplishments in hematological and endocrinological research using the techniques of nuclear medicine.

1973: Ludwik Gross, M.D., Senior Medical Investigator and Chief, Cancer Research Unit, VA Hospital, Bronx, N.Y., for outstanding accomplishments in oncogenic virus research.

THE VA MEDICAL RESEARCH PROGRAM

An abbreviated history

Medical research was first incorporated officially into the basic mission of the Veterans Administration's medical care program on September 2, 1958, when the Congress enacted Public Law 85–857, which so amended Title 38 of the U.S. Code that Section 4101 would henceforth read: ". . . The functions of the Department of Medicine and Surgery shall be those necessary for a complete medical and hospital service, including medical research."

Medical research was a very modest program in the VA at the end of World War II. Such medical research as existed at that time was almost entirely conducted by contracts with members of medical schools which were affilated with the VA. When the Congress made its first appropriation of VA funds earmarked for medical research in fiscal year 1955, the total research funding was a mere $4.8 million.

Greater promise seemed to lie in intramural research programs which were augmenting the medical research contract program, and in 1956 the contract program was entirely supplanted by intramural research projects. That first year in which the VA directed its medical research, individual research investigators reported on 3,644 research projects, and made enough progress to have 900 reports published in professional and scientific journals.

The early VA medical investigators were quick to discover and put to the test one of their most valuable assets—the cooperative study. In a cooperative study, investigators from any number of different VA facilities may agree to study a selected problem under uniform guidelines. The unique quality of VA cooperative studies is that the investigators may rapidly amass significant statistics by drawing upon the largest patient population available to any single agency in the Western World.

One of the earliest of these cooperative studies was initiated in 1946 in cooperation with the Armed Forces, to study the effectiveness of the chemotherapy for tuburculosis. The success of this study in determining the optimum medical treatment, caused the management of that disease to become so effective that the VA was able to close or convert all of its tuberculosis hospitals to general medical and surgical care. The cooperative study scored another major success in finding the most effective chemotherapy for treating neuropsychiatric patients which threatened to tax the VA neuropsychiatric (NP) hospitals beyond their capacity after the end of World War II. The success of this study enabled the VA to care for the NP patients in existing facilities at a time when it had been thought that the number of NP hospitals would have to be doubled at a cost estimate approaching a billion dollars.

The classic VA cooperative study on the benefits of treating mild hypertensive patients with antihypertensive medicine established the value of early treatment of high blood pressure in prolonging active, useful life and comfort in the Nation's aging population. Earlier findings showed that the risk of crippling or fatal strokes is directly

related to the height of a person's blood pressure, and that proper treatment now available will reduce the risk of having a stroke by 75 percent. This cooperative study is largely responsible for a National and probably world-wide mobilization of health care resources to find and treat effectively those persons who are developing even mild high blood pressure.

Medical research in VA facilities increased steadily in range and in accomplishments from the time it first became part of the total program of medical care for veterans. Since 1955, the Congress has made the following annual appropriations for medical research in the VA:

1957	$10,000,000	1967	$42,911,000
1958	10,344,000	1968	44,472,000
1959	15,344,000	1969	46,616,000
1960	17,344,000	1970	57,134,000
1961	21,500,000	1971	60,686,000
1962	27,000,000	1972	67,796,000
1963	29,500,000	1973	74,702,000
1964	32,572,000	1974	72,876,000
1965	36,508,000	1975	87,663,000
1966	39,983,000	1976	87,722,000

MEDICAL RESEARCH ADVISORY COMMITTEES

Merit Review Boards.—In fiscal year 1975, components of local hospitals' institutional research programs continued to be centrally reviewed by fifteen categorical Merit Review Boards. This process for establishing the scientific merit of major component programs formed a necessary part of local and National institutional program review and provided each hospital with a uniform basis for judging the quality of its programs and investigators for the most efficacious distribution of research funds. The extensive research program critiques and summary statements returned to hospitals provide an essential management tool for decentralized administration and are of value in central planning for research construction and analysis of need for research equipment and facilities and research staffing requirements. The support of a quality research milieu at the local level has served to support the patient care mandate of the VA and to recruit and retain quality clinical staff.

The Medical Research Career Development Committee (Consultant).—Comprised of non-VA medical and education specialists, acts as the selecting body for the positions of research associates, psychology research associates, clinical investigators, medical investigators, and senior medical investigators. In addition, the group makes the final recommendation on the William S. Middleton Award.

The Cooperative Studies Evaluation Committee.—Comprised of selected experts in the field of medical collaborative research, mostly research physicians with varying specialty backgrounds (phychiatry, surgery, internal medicine, etc.) and medical biostatisticians. It provides informed scientific evaluation of all cooperative studies as to their merit and validity, as well as professional evaluation of their relevance and importance to medicine and medical science.

(NOTE.—A listing of the above Board members and Committee members appears in Part II, Data Supplement.)

ADMINISTRATIVE DATA

The fiscal year 1975 Congressional appropriation for medical research in the Veterans Administration was $87,663,000. The amount of $1,167,000 was brought forward from the 1974 appropriation and estimated reimbursements of $4,540,000 increased the total available for the year to $93,370,000. Total program costs for the fiscal year were $91,627,000 including actual costs subject to appropriation reimbursements earned or received totalling $4,597,000. The distribution of total costs by research activity for the year was:

Institutional Research:	
Administration	$6,161,000
Common research support	5,522,000
Biomedical research projects	39,011,000
Other professional research	6,969,000
Animal research facilities	5,429,000
Special Research:	
Special laboratories or programs	856,000
Cooperative studies	6,752,000
Career development program	9,026,000
Other designated research	1,155,000
Minor alterations and improvements	875,000
Equipment:	
Construction projects	559,000
All other	9,311,000
Total costs	91,627,000

MEDICAL RESEARCH CAREER DEVELOPMENT PROGRAM

Through the Career Development Program the VA is able to attract and retain potential and experienced physician investigators. The physicians, dentists, and medical scientists in the program benefit in that they may systematically progress along avenues of their choice in research and clinical careers. Further the Career Development Program operates to the mutual advantage of the VA and affiliated universities by promoting intellectual cross-fertilization and by achieving optimal utilization of the facilities and educational resources of both institutions.

The spectrum of the career development program includes four levels; the senior medical investigator position is at the top, and is open to outstanding VA investigators of proven achievement who are expected to continue with excellence in research. The next rung of the career progression ladder is that of medical investigator, which provides an opportunity for physicians and dentists who have established themselves as successful investigators to pursue research and clinical activities in a targeted area of concern. The clinical investigator level is designed to encourage talented young investigators with an aptitude for research to supplement their medical knowledge and skill with an equal competence in the sciences and technology. The research associate level is designed for physicians and dentists who have demonstrated an interest and aptitude in research and wish to combine this with clinical skills.

Senior medical investigator program

The senior medical investigator program was initiated in January 1959. This program is designed to give recognition to senior physi-

cians and dentists who have distinguished themselves in research in the Veterans Administration and who give promise of continued productivity in research. These senior investigators are permitted to work independently on research of their own choosing. They may accept teaching and patient care responsibilities, but the primary focus is on their research activities and they are supported directly from research funds. Eleven distinguished investigators have been singled out for this appointment. Dr. Samuel H. Bassett, VA Center Los Angeles, California (deceased); Dr. Solomon A Berson, VA Hospital, Bronx, N.Y. (deceased); Dr. Oscar Auerbach, VA Hospital, East Orange, N.J.; Dr. Edward D. Freis, VA Hospital, Washington, D.C.; Dr. Ludwik Gross, VA Hospital, Bronx, N.Y.; Dr. Morton I. Grossman, VA Center, Los Angeles, Calif.; Dr. Paul Heller, VA Hospital, Chicago (WS), Ill.; Dr. Jay T. Shurley, VA Hospital, Oklahoma City, Okla.; Dr. Rosalyn Yalow, VA Hospital, Bronx, N.Y.; Dr. Sidney H. Ingbar, VA Hospital, San Francisco, Calif.; and Dr. Andrew V. Schally, VA Hospital, New Orleans, La. Each holds a professorship in his or her specialty with the affiliated medical school.

The findings of Dr. Auerbach's research on smoking and lung cancer are well known. More recently he has focused on emphysema and cardiovascular sequelae found after long-term cigarette smoking in animals and man.

Dr. Edward Freis is widely known for outstanding research on hypertension. Among many other activities, Dr. Freis is chairman of the VA's 16-hospital cooperative study of antihypertensive agents.

Dr. Ludwik Gross, a pioneer of modern research on the virus origin of cancer, is internationally known for his finding of cell-free transmission of leukemia in mice, the isolation and identfication of the mouse leukemia and the parotid tumor viruses. Dr. Gross was honored in 1975 by the Cancer Research Institute for his contributions to the field of cancer immunology. In 1974, he received the Albert Lasker Basic Medical Research Award.

Dr. Morton I. Grossman's major research activities have been in the fields of gastric and pancreatic physiology and the regulation of hunger and appetite. His current research is on the interaction of nervous and hormonal factors in the regulation of gastric and pancreatic secretion.

Dr. Paul Heller has distinguished himself by his research in disease of the blood, especially with reference to abnormal hemoglobins (such as seen in sickle disease) and in blood protein disorders. He heads the VA's 13-hospital cooperative study of sickle cell disease.

Dr. Andrew V. Schally is known for his accomplishments in isolating, determining the structure of, and synthesizing neurohormones of the hypothalamus, particularly thyrotropin releasing hormone (TRH) and leuteinizing hormone releasing hormone (LH–RH), all of which played a leading role in opening an entirely new and important field in neuroendocrinology. Follicle stimulating hormone-releasing hormone (FSH–RH) activity seems to be an intrinsic part of the LH–RH molecule.

Dr. Jay T. Shurley's research is on the nature of the brain-mind adaption of the individual to drastically altered or stressful environments. The preception and processing of information in man and the psychophysiology of sleep disorders and of sensory and perceptual isolation are two specific lines of investigation currently in progress.

Rosalyn S. Yalow, Ph.D. was the first non-physician to be appointed a senior medical investigator. Dr. Yalow's major research activities include radioactive labeling of biological compounds, radioimmunoassay of various hormones, metabolism of labeled biologicals, and related topics. In 1975 Dr. Yalow was elected to membership in the National Academy of Sciences.

Dr. Sidney H. Ingbar resigned as Senior Medical Investigator during fiscal 1975 to return to Harvard Medical School.

Medical investigator program

This program provides established successful investigators an opportunity to pursue research activities for a major portion of their time with the remaining time spent in teaching and patient care. Candidates selected will be those from whom the VA can anticipate continued productivity; they receive 6-year appointments.

A list of the scientists who served as medical investigators during fiscal year 1975, along with their hospitals and disciplines appears in Part II, Data Supplement.

Clinical investigator program

The Clinical Investigator Program is designed to provide a three year concentrated research experience for maturing physicians and psychologists.

The candidates for clinical investigator program are chosen from medical graduates and clinical psychologists who have extended their education by means of residency or similar programs. Successful candidates have also revealed an ability for significant research by postdoctoral research fellowship and additional research experience.

The names of the clinical investigators during fiscal year 1975, their hospitals and disciplines appear in Part II, Data Supplement.

Research associate program

The research associate program is principally designed to prepare physicians and clinical psychologists to bring advanced skills to bear on problems of particular importance in the care of veteran patients. Under the guidance of qualified preceptors the associates are encouraged to learn new technologies at their hospitals.

A list of those Research Associates who served, along with their hospitals and specialties, appears in Part II, Data Supplement.

Psychology research associates

The VA research associate program began as one for psychologists to enter careers as responsible investigators and soon developed to include many medical specialties. The psychology portion of the program continues today as a research experience for psychologists who evidence strong potential for research. There is broad opportunity for selection of the area of research interest and association with preceptors of acknowledged achievement and stature in the scientific com-

munity, laboratories engaged in psychophysiological, experimental, clinical, or social psychological research.

In fiscal year 1975, there was one psychology research associate in training. This is the last one who will be designated as psychology research associate. This portion of the program is being totally integrated into the Research Associate Program.

Advanced specialty training program

The clinical associate position was initiated in fiscal year 1968 in Advanced Specialty Training Programs. These training programs provide an initial clinical and research assignment of high quality specialty training for physicians and dentists who had completed two years on an approved residency or its equivalent. These programs are currently being phased out. A list of training programs and facilities appears in Part II, Data Supplement.

RESEARCH PROGRAM

The research program is designed to meet three major obligations. The first of these is to provide the best care for veterans. In meeting this need the research program has been used as a device to recruit physicians and other scientists. Since these individuals come largely from the academic world, such recruitment is heavily dependent upon the opportunity to conduct clinical research in a hospital setting. These research efforts, always highly individualized, must be integrated into a total research program which is balanced, particularly with reference to the patient population we serve. It would be impossible to do more than summarize the major thrust here. However, the clinical research summaries which follow will give some idea of the clinical care orientation and broad range of interest of our physicians.

It is also clear that the second responsibility, mainly that of providing our fair share of biomedical research effort for the good of the entire country, is being met consonant with the resources made available to us.

A final and very important obligation is to utilize the unique capability of the VA hospital system in answering questions which can only be answered by large numbers of patients under a single management. This capability is unique to the VA in this country and, when one considers that the number of patients treated exceeds that of some countries with nationalized systems, it is not surprising that our multihospital studies have received international attention. These are also summarized below.

HEALTH SERVICES RESEARCH AND DEVELOPMENT

The Health Service Research and Development Servie (HSR&DS) has continued to place emphasis on developing a program keyed to the most comprehensive and expeditious delivery of health care to patients in the VA system. During the year this program was restated in terms of the goals and objectives established by the Department of Medicine and Surgery (DM&S) management by objectives process,

thereby insuring integration of research and development plans with operating plans.

The development of criteria for the quality of care and of instruments to measure the degree of quality attained is a primary DM&S and HSR&DS goal. Sets of instructions, guidelines and instruments developed to assist in evaluating the quality of medical/surgical and mental care were issued during the year and distributed throughout the VA system to aid the hospitals in developing their individual systematic internal review programs for self-evaluation as part of the Health Services Review Organization (HSRO) program. On-going work includes refinement of existing HSRO tools and methodologies and the development of new ones for application in areas not yet adequately covered. Also, plans for the evaluation of the impact of HSRO are being developed, looking toward evaluation and revision of HSRO in a continuing program of improvement.

With the rapidly expanding demands for ambulatory care, a number of projects have been supported that look to appropriate and efficient patient treatment prior to, or in lieu of, hospital admission. These projects often take the form of development, pilot test and evaluation of innovative health care delivery models. Modeling activities have included projects such as the prototype Preadmission Psychiatric Assessment Unit developed at the VA Hospital, Salt Lake City, Utah for evaluating the physical, psychological and social status of applicants for mental health care prior to their admission to or treatment at the hospital.

This system for collecting data on, and assessing the condtion of, patients proved successful and was incorporated into the regular operation of the hospital at the completion of its pilot stage this year. A formal cost and effectiveness evaluation is now being conducted to determine the "exportability" of the model to other hospitals.

Similarly, a project begun last year to develop and test clinical algorithms for diagnosis and treatment of simple acute illnesses will lead next year to pilot testing of the algorithms as an integral component of a functional ambulatory care model at the VA Hospital, Tucson, Arizona, and possibly at other hospitals.

In the area of hospital functions and services supporting direct patient care, recent studies include such varied subjects as cost-benefit analysis of manual and computerized patient appointment scheduling systems; pilot test of a semiautomated system for preparation of radiology reports; and initial development of a nation-wide on-line pharmacy information system that can provide patient medication history as well as the usual pharmacy inventory and control functions.

Work on the planned integrated clinical and administrative hospital information system began with the initial steps to identify and define the fundamental data elements required in the operation and management of medical districts and their component hospitals under the regionalization concept now being implemented.

The VA is cooperating with the National Center for Health Services Research of the Department of Health, Education and Welfare in two programs intended to encourage research and development in health services and to train personnel appropriately for such work. The National Center for Health Services Research will fund a number

of grants for the establishment of Health Services Research Centers in academic institutions having working relationships with health service delivery settings.

To encourage VA hospital participation, HSR&DS has offered, to each VA health care facility that successfully participates with a university in applying for and obtaining a Health Services Research Center grant, funding to provide manpower for active participation by the hospital. Similarly, Education Service and HSR&DS have entered into a cooperative arrangement with the National Center to help provide interdisciplinary education and training in health services research to selected trainees. Each trainee will be expected to have a health care background and to be working for a Ph.D. in an approved educational institution. Those students who successfully complete the program will be offered VA employment in a variety of suitable positions through which they may be able to influence favorably VA health care delivery.

PROSTHETICS RESEARCH

The Prosthetics Research Study, Seattle, Washington, tested a controlled environment treatment developed in England. This treatment is intended to expedite healing of freshly amputated limbs. Though it does not allow immediate prosthetic fitting and ambulation, replacement by a rigid socket and intermediate prosthesis is possible after 10 days.

The VA Prosthetics Center, New York, N.Y., has developed a myoelectrically controlled electric hook capable of unusually high grasping force. Several prototypes are under evaluation.

Cooperative studies were conducted involving possible prevention of amputation for peripheral vascular disease or at least amputation as distally as medically feasible. The Seattle Study, operating at the VA and other hospitals, and the VA Hospitals at San Francisco, Calif., and Castle Point, N.Y., have found increasing success in healing after amputating not only below the knee but often at the ankle, in contrast to many texts which teach amputation through the thigh. Patients with more distal amputations, treated by immediate postsurgical prosthetics management, are more rapidly rehabilitated and discharged. Even the prosthesis costs substantially less than an above-knee artificial limb.

Experimental prototypes of a unique combination power bed-wheelchair were demonstrated during the year. They allow a quadriplegic independent mobility within a hospital or a ranch-style home and patio.

Several ambulators are being designed to enable a patient who cannot stand independently to work in the upright position and to move voluntarily for short distances on level surfaces. These will allow activities in a kitchen, bathroom, office, or at a public telephone, especially where narrow passages limit a wheelchair.

Clinical studies on mobility and reading aids for the blind and partially sighted continued at the three Blind Rehabilitation Centers. Western Michigan University, with VA education funds, conducted a series of courses for orientation and mobility instructors on two ultra-

sonic aids and on the VA-supported laser cane. This new pool of skilled instructors will expedite transition from evaluation to wider clinical use by blinded veterans and others.

CLINICAL RESEARCH

Aging

The Veterans Administration has recognized the importance of research on the varied aspects of aging by establishing Geriatric Research, Educational, and Clinical Centers. These new Centers embrace research in basic and in clinical areas. Investigations on the problems of aging are conducted also at other VA health care facilities; some dealing with medical and psychiatric conditions in aged persons are summarized under other headings.

In a longitudinal interdisciplinary study of normal aging conducted at the VA Outpatient Clinic (OPC), Boston, Mass., a composite index of functional aging was developed. It was based on a dozen biological and behavioral measures which together accounted for about 65 percent of the variability in chronological age of more than 900 men aged 26–83 years. Recent information from the same study indicates that the value of such functional measures, designed to predict both rates and stages of aging, probably will be limited to narrow age ranges. Different systems age at different rates and most do not change uniformly across the adult age range. For example, the preferred age of retirement stays relatively constant until age 50 after which it shows a substantial increase. In contrast, pulmonary function declines at an increasingly slower rate with old age. In some older groups, pulmonary function even increases slightly over ten years, due to changes in smoking and exercise habits.

Medical data, information on life style, personality and other behavioral characteristics are available for participants in the Boston OPC Normative Aging Study, making it possible to identify several factors which modify patterns of aging. For example, the effects of smoking on pulmonary function, in comparison to those of age are quite small and remain about the same across the adult age range.

Other information relating weight loss and smoking in the same volunteers indicates that almost 40 percent of the men who quit smoking do not incur long-term weight gains. The data suggest that the frequently reported finding of weight gain following the cessation of smoking fails to take into account normal weight changes.

It has been possible to employ measures of three dimensions of personality: anxiety-adjustment, introversion-extroversion, and openness to experience to identify various reasons for smoking and to study the relation between anxiety and cognitive functioning in several age groups.

At the VA Hospital, Topeka, Kansas patients with diffuse brain damage and normal controls in two age groups were administered a large battery of mental tests. In the older group the performance differed as much between the normal and brain-damage subjects as it did in the younger group, contradicting the hypothesis that the effects of aging on cognitive functioning resemble those of brain damage.

Functioning of the nervous system may decrease with age because the delivery of oxygen to the cells is deficient or because they cannot use oxygen efficiently. This hypothesis is the basis for the experimental use of hyperbaric oxygen therapy at the VA Hospital, Buffalo, N.Y. An investigator at the VA Center (Wadsworth) Los Angeles, Calif., working in collaboration with a Navy scientist, found that this technique improved short-term memory and visual organization in subjects who scored poorly on the Wechsler memory scale. Although these results are encouraging for both practice and theory, fully-controlled studies of the relationship between cognitive functioning and oxygen therapy are lacking.

Investigators at VA Center (Brentwood) Los Angeles, Calif., have confirmed the existence of age differences in chromosome abnormalities in cultured leukocytes. More were found in cells from elderly women than in those from young and middle aged adults.

At the Oklahoma City VA Hospital, patients with senile dementia associated with atheroclerosis were given sufficient zinc sulphate to raise the average plasma zinc concentration by about 80 percent over a 24-week period. Compared to untreated controls, the patients showed no significant differences in physiological functioning, blood chemistry, electroencephalograms or behavioral measures. Zinc sulphate administration did not improve cerebral functioning.

Senile dementia with ataxia and incontinence can be due to normal pressure hydrocephalus, an unusually large accumulation of fluid in the cranium. VA clinical researchers at Boston and Minneapolis are engaged in evaluating surgical procedures for correcting this abnormality.

Normal age differences in memory and cognitive processes continue to receive attention from VA scientists. At the VA Hospital, Syracuse, N.Y., retention for short lists of digits was superior when they were presented auditorily rather than visually; the opposite was true for prose. The modality effects were the same for young and old subjects.

Two lines of research at the Boston OPC indicate that age differences in very long-term memory are quite small. In one study, retention for pictures viewed under standard conditions was assessed immediately after viewing the pictures and again after intervals ranging from 4 weeks to 2½ years. Retention declined at about the same rate for all subjects and remained above a chance level after the longest interval. In the other study, no age deficits were found in the retention of popular information associated with earlier events, personalities and sayings.

Age differences in the metabolism of the circulatory system were studied at the VA Hospital, Seattle, Wash. using tissue cultures of smooth muscle from the arterial wall. The uptake of lipoproteins in cultured cells did not change with the age of the donor. However, attempts to stimulate the growth failed when cells were relatively old in cultured life. The research suggests that the gradual accretion of lipids in the smooth muscle cells is a normal phenomenon. In other research, the investigators are comparing the lipid uptake of normal and diabetic patients to evaluate the hypothesis that the effect of diabetes is functionally equivalent to that of normal aging.

At the VA Hospital, San Francisco, Calif., the morphological structure of the livers of virgin male rats was compared to that of retired

breeder rats with hyperlipidemia, arteriosclerosis and a shortened life span.

The livers of older rats had a greater relative volume of lysosomes and the parenchymal cells were larger. These differences were largely obliterated by administrating a synthetic anabolic steroid. The investigators concluded that the age differences are not the result of irreversible alterations on the genome or in the translation transcription apparatus.

At the VA Hospital, Cincinnati, Ohio, investigators found that the incidence of lymphocytotoxins in men and women increased with age, the increase being greater in the 60's and 70's than in the 20's through the 50's. The results reflect minor histocompatibility reactions consistent with the autoimmune theory of aging.

Studies of age differences in the composition of blood serum indicate that serum copper concentration increases very slightly between the ages of 20 and 80 years in males but not in females. Serum ceruloplasmin on the other hand did not increase.

Bone and connective tissue continues to receive attention. At the VA Hospital, Martinsburg, W. Va., two collagen cross-link ages have been identified in the rat uterus and their relationship to age determined.

Investigators of the VA Hospital, Sepulveda, Calif., studied the properties of mitochondrial DNA in sea urchin eggs and in embryos containing 4 to 200 cells. The mitochondrial population of dividing and non-dividing mature cells is believed to be continuously removed; disturbances in this replication could cause dysfunction or death in aging cells.

Alcoholism and Drug Dependence

Drugs

Extensive research on drugs with abuse potential was performed at VA Hospitals in fiscal year 1975. The results will improve the psychological assessment and therapy of drug dependent patients as well as increase knowledge of the mechanisms of action, metabolic effects and adverse reactions of these drugs.

At the VA Hospital, Philadelphia, Pa., investigators reported on the sexual problems of *heroin addicted* and *methadone maintained* veterans, emphasizing the frequency of such problems.

Investigators at the VA Hospital, Wood, Wis., designed and tested a rating scale which enables physicians to assess the degree of *narcotic* addiction in drug dependent patients. A clinical trial showed the rating scale to be accurate and to be useful in the treatment of narcotic withdrawal.

In other studies at Wood, Wis., morphine was found to have an effect on cellular respiration. The pain-killing effect of morphine apparently is not due to this effect because other similar pain-killing drugs (methadone and pentazocine) do not have the same cellular action.

Two studies, conducted at the VA Hospital, Palo Alto, Calif., have added to knowledge of delta-9-tetrahydrocannabinol (the active ingredient of *marijuana*). In one, a new technique for detecting delta-9-THC in the urine was developed; in another, the effects of delta-9-THC on blood sugar and on some of the hormones which control blood

sugar were investigated. Large doses of delta-9-THC given by vein impair the normal mechanisms for clearing excess sugar from the blood. At doses achieved by inhalation, however, this effect is minimal.

In another study, also at Palo Alto, the use of propranolol (a widely used drug for cardiovascular disease) in the treatment of withdrawal from narcotics was assessed. Although previous studies suggested that propranolol was a narcotic antagonist, no such action was found. Propranolol did give some symptomatic relief during narcotic withdrawal but not enough to outweigh the potential harmful effects of the drug.

The effect of barbiturates on the metabolism of norepinephrine, a normal chemical compound in brain and nerve tissue, was studied by investigators at the VA Hospital, Houston, Texas. They demonstrated that breakdown products of norepinephrine were altered both in amount and in quality, providing insight into the action of barbiturates on the brain.

Alcohol

Many investigators at VA Hospitals have focused on the metabolism and toxicity of alcohol and the complications of alcoholism. Only a few of the published studies can be mentioned.

At the VA Hospital, Bronx, N.Y., alcoholic disease was the subject of a multi-faceted approach. In rats, a good animal model for the early stage of alcoholic liver disease, acetaldehyde (the first breakdown product of alcohol) reached a significantly higher blood level in alcoholics than in nonalcoholics given the same amount of alcohol. Since acetaldehyde is toxic for liver, heart and brain, this observation may explain some serious complications of alcoholism. Acetaldehyde is normally burned by the cell's mitochondria, a function damaged after chronic alcohol consumption.

Studies of more advanced liver disease were accomplished in the baboon and have now been completed; they document the production of alcoholic hepatitis and even cirrhosis in baboons fed alcohol chronically. This model has given the best approximation of human alcoholic disease and, hopefully, its use should improve understanding of the development and treatment of severe complications of alcoholism. Effects of alcohol on organs other than the liver were also studied including damage to the small intestine caused by large doses of orally administered alcohol.

A study of the VA Hospital, Cincinnati, Ohio showed that the acute administration of alcohol, in moderate doses, enhances absorption of fat by the small intestine.

At the VA Hospital, Togus, Maine, a clinical evaluation of lithium therapy in alcoholic veterans indicated that the metal had a marked beneficial effect on the drinking habits of alcoholics. The effect of lithium was not due to its anti-depressive properties, but, regardless of its mechanism, the regimen appears to be potentially useful.

Investigators at the VA Hospital, Indianapolis, Ind., found abnormalities in vitamin B_6 metabolism which they attributed to the direct action of acetaldehyde, the major breakdown product of alcohol.

An investigator at the VA Hospital, Albuquerque, N.Mex., reported that white blood cells from alcoholic patients behaved as im-

mature cells due either to vitamin deficiency or to the direct toxic effect of alcohol. This may help explain the increased incidence of infection of alcoholic patients.

The psychologic aspects of alcoholism were widely investigated at VA hospitals during the past year. In one such study, a new approach to alcoholic patients was taken at the VA Hospital, Coatesville, Pa. Alcoholics in the treatment program chose whether they would continue to drink without fear of being expelled from the program or would stop. About half chose not to drink and half of those who chose to drink stopped during the treatment period. It became clear that patients who abstained had a better prognosis for treatment than those who did not.

Audiology and speech pathology

Investigators at the VA Hospital, Minneapolis, Minn., have differentiated four types of aphasic patients who were formerly pooled under one heading of "auditory comprehension problems." The investigators reported typical test scores for each of these patient categories and indicated therapeutic techniques specifically designed for each. Data from this study provide the means for more efficient, effective speech therapy for the long-term aphasic patient.

In the same vein, a research report from the VA Hospital, Cleveland, Ohio, assessed the capabilities of the most severely impaired aphasic patients to comprehend verbal instructions. These investigators have proposed new criteria for evaluating responses from global aphasic patients to tease out selective factors that are still operating in the communication link from comprehension to expression.

Research at the VA Hospital, St. Louis, Mo., has focused on evaluating the teaching of American Indian sign language to patients with various types of severe oral communication disorders. Patients using this type of sign language demonstrated marked improvement on verbal test items suggesting that the language stimulation by signing facilitated the verbal output of these patients. It was also found that untrained viewers could read Indian signs.

Research at the VA Hospital, Syracuse, N.Y., added to the growing body of literature on the effects of acupuncture on nerve deafness. The investigators, using double-blind techniques on two matched groups of hearing-impaired adults, found that those subjects receiving acupuncture treatments at the body site designated for hearing showed no difference in their test results using standard audiometric evaluation techniques.

In the control group, some subjects received up to 8 control treatments in sites not related to hearing or deafness, such as those for gastrointestinal changes. This group had no significant audiometric changes over the course of the study. Subjective reports from a number of the study subjects did indicate improvement in their hearing, particularly for background noises.

Cardiovascular disorders

The effect of environmental pollutants on patients with cardiovascular disorders has been of substantive importance to investigators in the VA for the past several years. Thus a study at VAH, Long

Beach, Calif., showed that cigarette smoking and breathing carbon monoxide by patients with angina pectoris produced the reported cardiovascular hemodynamic changes during smoking of nicotine-containing cigarettes including elevated blood pressure and heart rate. Depression of the heart's ability to contract was related not to the nicotine content but rather to the presence of carbon monoxide in the inhaled smoke. These observations further delineated the deleterious effects of smoking on patients with angina pectoris.

Physicians have long suspected that cigarette smoking reduces blood flow in the extremities but it has not been clear whether the cause was the smoking *per se* or the associated deep inspirations. A group of investigators at the VA Hospital, Allen Park, Mich., demonstrated that blood flow is reduced by approximately 50 percent in the lower extremities and that the cause is the inhalation of the smoke from cigarettes, not the associated deep breathing.

Investigators at the VA Hospital, Bronx, N.Y., reported the responses of industrial physicians who were asked whether they would hire patients with various cardiovascular, pulmonary and psychiatric illnesses. Despite great strides in treatment and rehabilitation, the physicians expressed a considerable, though variable, reluctance to hire patients with myocardial infarcation, angina pectoris, rheumatic heart disease, hypertension, renal disease, diabetes, tuberculosis and previous psychiatric illness. A concern for liability for further illness and a possible increase in the cost of compensation insurance were contributing factors in more than 85 percent of the negative responses.

The kidneys of individuals from industrialized areas contain more cadmium than do those of persons from underdeveloped nations. Cadmium has been considered to be a potential source of cardiovascular disorders. Investigators at the VA Hospital, St. Louis, Mo., have developed a new and sensitive technique for determining cadmium in the blood and urine called Graphite Furnace Atomic Absorption Spectrophotometry. This should prove valuable in further assessing the role of cadmium in human cardiovascular disorders.

Also at St. Louis, VA investigators found that the height of the diastolic hypertension is positively related to the degree of cognitive dysfunction as measured by a psychological test used to diagnose brain damage. Thus high blood pressure not only increases the risk of strokes and transient ischemic attacks but can also adversely affect the mental acuity of patients whose blood pressure remains consistently in the hypertensive range.

Investigators at the VA Hospital, Cleveland, Ohio, studied the effects of an enzyme that converts angiotensin to its active form, demonstrating that the enzyme also hydrolyzes bradykinin and its higher homologues. Bradykinin is a substance associated with physiologic changes during inflammation. Enzymes that degrade it could therefore control the extent of inflammatory reaction.

Atherosclerotic heart disease

Mass screening for coronary risk factors was performed in more than 2,500 asymptomatic adults in southern California. The prevalence of elevated serum cholesterol, increased triglycerides, hypertension,

cigarette smoking, early signs of diabetes and obesity was confirmed in this subset of the population and high incidence of abnormal EKG's was found. This study emphasizes the importance of physician follow-up. Of equal importance is transmitting results to the patient and providing him with enough information to act intelligently in reducing his risk of coronary atherosclerosis.

The VA Cooperative Drug Lipid Study was the first to attempt to answer the question of which drugs effectively lowered serum cholesterol. A derivative of nicotine acid, aluminum nicotinate, was shown to reduce cholesterol levels whereas estrogen did not. Although the sustained cholesterol-lowering effect of dextrothyroxine was reaffirmed, the agent is no longer used because of its potential cardiotoxicity.

In another report, the long-term effect of a drug, halofenate, was described. This drug does not significantly affect mean serum cholesterol levels, but is of value in treating hypertriglyceridemia and hyperuricemia, the former being identified as a secondary risk factor in atherosclerotic heart disease and the latter being a common accompaniment.

Findings were reported on the effects of a new agent, tolamolol, on the cardiac function of patients with angina pectoris. Tolamolol is a beta-blocking agent which has more effect on the cardiac beta receptors than on those in other organs and hence causes fewer side effects, particularly in patients with coexisting pulmonary disease. This agent produced a 25 percent increase in exercise time in some, but not all, patients with angina pectoris.

VA investigators were also able to demonstrate an effect of sublingual nitroglycerin on myocardial function in patients with coronary artery disease. Many patients with coronary artery disease have areas of the heart that contract poorly. Sublingual nitroglycerin improved the ability of the heart muscle to contract, as measured by ventriculography, presumably because it relieved myocardial ischemia.

Basic science research

Contributions to the understanding of cardiovascular disturbances were made through research in the biochemistry or physiology laboratories when direct investigations on human subjects were inappropriate. A series of investigations at the VA Hospital, Durham, N.C., increased understanding of myocardial blood flow during exercise and ischemia. The investigators utilized new techniques that permitted measurements in the awake, active animal and compared these to studies in the same animal after anesthesia and chest surgery thus illustrating the dangers of extrapolating data from anesthetized, thoracotomized animals to awake, active animals. The amount of blood flowing to the endocardium, an area particularly vulnerable to myocardial ischemia and infarction, was measured in awake animals at rest and during exercise.

Cardiac denervation did not impair the ability of coronary vasculature to respond to brief periods of ischemia, demonstrating the importance of local factors in the control of coronary vascular resistance by determining myocardial blood flow distribution during ischemia in the unanesthetized animal. The investigators demonstrated that with significant coronary stenosis, ischemia-induced coronary vasodilation resulted in redistribution of the flow away from the subendocardial region leaving it vulnerable to myocardial damage or infarction.

Myocardial function in shock was explored by investigators at the VA Hospital, Oklahoma City, Okla. The presence of a circulating myocardial depressant in shock has been postulated but the investigators were unable to demonstrate impairment of function by depressant factors circulating through the heart from an ischemic splanchnic region. With endotoxin shock, marked myocardial depression was demonstrated.

A number of studies dealt with biochemical or electrophysiological aspects of the heart and blood vessels. A report from the VA Hospital, Philadelphia, Pa., emphasized the importance of vessel wall disturbances of lipid metabolism in the production of atherogenesis. Metabolism of fatty acids by aortic mitochondria was altered by cholesterol feeding and this may lead to increased esterification of cholesterol. Esterified cholesterol has a reduced exchange potential and thus may remain "trapped" in the aortic wall.

The effect of ischemia on the conducting tissue of the heart was evaluated in animals by investigators at the VA Hospital, Miami, Fla. They observed that, although the conducting tissue in the subendocardial regions are early affected by infarction, many Purkinje cells apparently resist, survive the infarction and return to normal function.

Investigators at the VA Hospital, Madison, Wisc., studied the effects of myocardial ischemia on intermediary metabolism in the heart. Ischemia decreases fatty acid oxidation and this may lead to an accumulation of substances that inhibit the metabolism of adenine nucleotides. The net result would be a lower energy charge of the cell with diminished muscle contraction and electrical condition in the ischemic myocardium.

Investigators at the VA Hospital, Minneapolis, Minn., developed evidence that the myocardial cell concentration of calcium is related to stimulation of RNA and protein synthesis thus extending knowledge of the effect of catacholamines which increase intracellular calcium concentration on RNA and protein synthesis. This may help explain the influence of autonomic nervous system activity on RNA and protein synthesis.

An investigator at the VA Hospital, Houston, Texas, developed a new technique for measuring beat-to-beat movement of calcium ions across the cell membrane, a tool that enables one to define more precisely the site of action of drugs that significantly affect myocardial contractility.

Several studies dealt with the control of the peripheral circulation. Investigators in the VA Hospital, Iowa City, Ia., demonstrated the regional vascular effects of vasopressin, a hormone produced by the posterior pituitary. The hormone had significant effects on blood vessels in the muscle, mesentery and kidney.

Cardiovascular surgery

The coronary artery bypass is one of the most frequent cardiovascular operations. The question remains as to which type of graft is better, the internal mammary arterial or the aorto-coronary venous graft. Investigators at the VA Hospital, Palo Alto, Calif., reported experience with both types of grafts in animals fed normal and hyperlipidemic diets. The internal mamary arterial grafts and better long-term patency; in the normal lipemic condition, the arterial grafts underwent less histologic change; and both types of grafts were more

susceptible to atheromatous change than the host's vessels. They are also investigating the problem of ischemic myocardial injury in human operations when the aortic valve is replaced and a coronary artery bypass graft is inserted. In many hospitals, the mortality rate for the combined operation is much higher than for either operation alone. Similarly, evidence of ischemic myocardial injury is higher in the combined operation.

Serum enzyme changes are important indicators of myocardial damage and minimal elevation of the serum enzymes can occur following cardiac catheterization and coronary angiography when myocardial damage may result. Investigators associated with the VA Hospital, Houston, Texas, evaluated serum enzyme changes following cardiac catheterization and coronary angiography. The values did not increase signficantly following these procedures except when intramuscular medications were given.

A therapeutic dilemma faces the cardiologist whose patient has chronic bifascicular block. Investigators at the VA Hospital, Chicago (WS), Ill., investigated the significance, mechanisms and clinical implications of chronic bifascicular block and demonstrated the specific indications for which pacemaking is required. The problem has now been put in clinical perspective and the initial enthusiasm for using pacemakers in all of these patients has been tempered through this careful analysis.

Investigators at the VA Center, Hampton, Va., described the hemodynamic effects of ethaverine hydrochloride on patients with peripheral vascular disease. A significant increase in muscle blood flow occurred in patients with atheromatous obstruction, suggesting that this agent might benefit these patients.

Clinical experience with pericardial infusion in uremic patients was reported from the VA Hospital, Nashville, Tenn. This common and frequently resistant form of pericarditis was effectively treated under certain circumstances by pericardiectomy.

Atherosclerotic heart disease and its complications

Complications of acute myocardial infarction include shock, congestive heart failure and cardiac arrhythmias of which the latter is by far the most common and potentially lethal. Prediction of one lethal arrhythmia, ventricular tachycardia, has been based on certain characteristics of ventricular premature beats. A group of investigators at the VA Hospital, Little Rock, Ark., have shown that the degree of prematurity of the ventricular premature beat in fact does not correlate well with the subsequent development of ventricular tachycardia. This observation may help prevent recurrent ventricular tachycardia and lead to better understanding of its pathogenesis.

Investigators also characterized the arrhythmias that occur during the course of acute myocardial infarction. One arrhythmia previously thought to be uncommon accelerated ventricular rhythm, was present in nearly 50 percent of patients. Furthermore, it did not always indicate a benign prognosis.

At the VA Hospital, Dallas, Texas, investigators further characterized some of the hormonal changes that occur during acute myocardial infarction. Serum glucagon levels rose significantly, particularly in patients with infarction and shock. The increase in blood sugar

found in patients with shock complicating myocardial infarction was related to this rise in serum glucagon and to a relative insulin deficiency.

Atherosclerotic heart disease involves predominantly the left ventricle and many assume that right ventricular dysfunction, as a *direct* result of atherosclerotic heart disease, is distinctly unusual. Three findings by VA investigators in Miami and Washington, D.C., suggest that, under certain circumstances, right ventricular function is directly impaired in atherosclerotic heart disease. The Miami investigators documented the incidence of dysfunction of the right ventricle in coronary artery disease. The Washington, D.C., VA investigators noted the association of right ventricular infarction with diaphragmatic infarction of the left ventricle. These clinical observations were supported by laboratory investigations in which significant right ventricular dysfunction was produced in an experimental animal.

Also, investigations at the Washington, D.C., VA Hospital into afterload reduction in the treatment of heart failure helped pioneer research into another aspect of cardiovascular disease. Results of one study indicate the importance of arterial pressure as a determinant of left ventricular filling pressure after acute myocardial infarction. Another study extends the concept of afterload reduction to the treatment of refractory heart failure in 18 patients with chronic intractable decompensation secondary to ischemic heart disease and cardiomyopathy; nitroprusside infusions significantly improved both hemodynamics and symptoms.

Graphic techniques

VA investigators continue to play leading roles in electrocardiography and vectorcardiography. Two investigators from the VA Hospital, Washington, D.C., described the diagnostic usefulness of frontal plane QRS loop rotations in the Frank vectorcardiogram in over 1,000 cases and the usefulness of computer analysis of the orthogonal electrocardiorgram and vectorcardiogram in mitral stenosis.

Other VA investigators have studied echocardiography in the diagnosis of cardiovascular disorders. They described the echocardiographic manifestations of flail aortic leaflets in bacterial endocarditis, and reaffirmed the usefulness of echocardiography in the diagnosis of pericardial disorders.

Investigators at the VA Hospital, Salt Lake City, Utah, described the simple, safe, noninvasive technique of plethysmographic monitoring in patients undergoing vascular reconstruction, sympathectomy and injection of chemical vasodilators.

Others, at the VA Hospital, San Diego, Calif., described the utility of ballistocardiography as a technique to compare cardiovascular events in a variety of species, including mouse, man and the whale.

VA investigators described the usefulness and the limitations of the 3rd and 4th heart sounds in the evaluation of patients with cardiovascular disorders.

Measurement of the *severity* of stenosis in heavily calcified aortic valves was accomplished by investigators at the VA Hospital, Oklahoma City, Okla., using measurements obtained from plain film orifice-view roentgenograms, a simple and safe noninvasive procedure.

Investigators at the VA Hospital, Denver, Colo., described a tech-

nique for measuring the left heart ejection fraction and end-diastolic volume by a computerized, scintigraphic technique utilizing a wedged pulmonary arterial catheter and technetium-99m.

Endocrinology and metabolism

Diabetes mellitus

Major progress in the understanding of diabetes mellitus continues to be made through studies at several VA hospitals especially on the role of glucagon. The advances began with the development of radioimmunoassays for insulin at the VA Hospital, Bronx, N.Y. The assays revealed that insulin secretion may be slow in adult onset diabetes but the absolute levels of insulin can be elevated rather than depressed. Development of the first successful glucagon assay at the VA Hospital, Dallas, Texas led to the discovery that an elevation of glucagon is a characteristic of diabetes mellitus. More recently the Dallas studies were extended to show that hyperglucagonemia is a characteristic of all types of glucose elevation.

Elucidation of the role of glucagon in the development of diabetic hyperglycemia was made possible by the discovery of another hormone, somatostatin, simultaneously at the VA Hospital, New Orleans, La., and at the Salk Institute. This hormone was soon shown to decrease the secretion of both glucagon and insulin. With the aid of somatostatin VA investigators at Dallas have now found thta glucagon plays an *essential* role in the development of diabetic hyperglycemia. In fact, if glucagon is suppressed it is not possible to produce an elevation in blood glucose despite the complete absence of insulin. It is becoming increasingly likely that glucagon is a key hormone in the development of diabetes. Moreover, with means available for suppressing glucagon, these new discoveries open the way to new approaches to the treatment of diabetes.

It had been assumed that glucagon is secreted only by pancreatic cells but the Dallas investigators have now shown that, in the absence of the pancreas, glucagon secretion is increased rather than depressed. Large amounts of glucagon can be produced by cells located in the stomach and the upper intestine. The importance of this *gastrointestinal* glucagon in the production of the diabetic syndrome is the subject of active study.

Investigators at the VA Hospital, Memphis, Tenn., have reported the most complete studies yet available on the treatment of diabetic ketoacidosis using low doses of insulin rather than the conventional high-dose therapy. This treatment of diabetic ketoacidosis is simpler, safer, and just as effective as high-dose therapy.

The finding that diabetics may secrete insulin at slower than normal rates but reach higher than normal absolute levels of insulin in adult onset diabetes has been explained by VA investigators at Palo Alto, Calif. The hyperglycemia of diabetes may be due in part to resistance of various diabetic tissues to the effects of insulin. They reported evidence of such insulin resistance emphasizing a little-recognized aspect of the diabetic syndrome. The Palo Alto investigators further indicated that the resistance of diabetic tissues to insulin may be due to a decrease in the numbers of binding sites for insulin on the surface of the individual cells of the diabetic.

Studies of diabetic vascular disease are continuing at a number of VA institutions, particularly at Dallas, Texas and San Francisco, Calif. Most patients with inherited diabetes have a thickening of the portion of their capillaries known as the basement membrane, a lesion apparently specific for genetic diabetes in the adult. Recent collaborative studies between the Dallas and San Francisco VA Hospitals have shown that this characteristic capillary lesion of diabetes is not seen regularly in diabetic children. The vascular abnormality is almost always present by the time the diabetic reaches adulthood, suggesting that effective prophylaxis of diabetic vascular disease should be concentrated in the childhood years.

Calcium and bone disease

Rapid progress has been made in the field of bone metabolism, particularly in the area of parathyroid hormone abnormalities. Routine screening for elevated serum calcium has disclosed abnormalities in the hormones, particularly parathormone and calcitonin, that control calcium levels and bone metabolism. Hormones produced by parathyroid tumors often cause bone disease but lung cancers can make a hormone that acts like parathyroid hormone. The commonest cause of elevated calcium levels in the age group seen in VA hospitals is cancer, particularly of the lung.

VA investigators at San Diego, Calif., have pioneered the development of sensitive methods for measuring parathyroid hormone and have more recently shown that they can differentiate true parathyroid hormone from the substance produced by cancer cells. Such measurements of specific hormones can be used as a means of early diagnosis of both parathyroid tumors and lung cancer.

Recent studies at the VA Hospital, Chicago (WS), Ill., have indicated that many common drugs, such as aminophyline used to treat asthma, may markedly influence parathyroid hormone secretion. The investigators have also demonstrated that in usual doses, steroid hormones may have a similar effect on parathyroid hormones.

Recent interest in calcitonin, another hormone influencing calcium metabolism, has increased greatly. Again the Endocrinology Unit at the VA Hospital, San Diego, Calif., has perfected methods for measuring calcitonin and has developed a simple, sensitive test for discovering calcitonin secreting tumors. Studies both in San Diego and at the VA Hospital, Indianapolis, Ind., have used either isolated thyroid glands or calcitonin-producing cells in tissue culture to examine the fundamental mechanisms by which calcitonin secretion is controlled. These studies have made it possible to study the control of calcitonin synthesis and have demonstrated that calcitonin is first synthesized as a pro-hormone which is later converted into the active compound.

These fundamental studies, coupled with their prompt clinical application are rapidly improving diagnostic and therapeutic approaches to the bone diseases in veterans.

Atherosclerosis and lipid disorders

The basic causes underlying the accumulation of cholesterol and triglycerides in the blood and arteries are being studied by investigators at the Palo Alto VA Hospital. Their evidence supports the concept that a high triglyceride level in man is frequently caused by

elevated levels of insulin and that diets high in carbohydrate may produce hypertriglyceridemia through such an insulin-stimulating mechanism. The increase in triglycerides seen in mild, adult onset diabetics may likewise be due to an absolute excess of insulin. This increase in triglycerides may predispose the diabetic to develop premature atherosclerosis.

Fundamental studies of cholesterol disorders in man at the VA Hospital Center, Los Angeles (Wadsworth), Calif., indicate that white blood cells from patients with an inherited form of hypercholesterolemia have a defective control mechanism for regulating cholesterol synthesis. One cause of atherosclerosis in man may be detectable simply by studying cholesterol synthesis in readily obtainable blood samples. The Wadsworth investigators have also discovered a new pathway by which the major building blocks of cholesterol can be converted to carbon dioxide. This may constitute a means by which the body controls the synthesis of cholesterol.

Alcoholism

One of the most serious complications of acute alcoholism is a sudden lowering of the blood glucose leading to convulsions and death. The mechanism is unknown but alcoholic hypoglycemia could be due to a reduced ability of the liver to synthesize glucose. Studies from the San Francisco VA Hospital have, however, demonstrated that the initial effect of alcohol is to increase glucose utilization rather than decrease glucose production. This effect is more marked in thin than in obese individuals.

Arthritis

Studies at the Wadsworth VA Hospital have shown that certain cell surface antigens are related to specific types of arthritis in man. Patients with crippling arthritis of the spine, called ankylosing spondylitis, have an extremely high incidence of cell surface antigen termed HLA/W–27. Patients with the arthritis that accompanies psoriasis and arthritis which accompanies urethritis and inflammation of the bowel likewise have a high incidence of HLA/W–27. This has made it possible to use the HLA test to diagnose previously unrecognized forms of arthritis and thereby to treat the disease before it cripples the patient.

Discovery of the relationship between psoriasis, inflammatory bowel disease, urethritis and ankylosing spondylitis suggests a common underlying cause of these conditions which previously had been assumed to be unrelated. Discovery of the relationship between HLA/W–27 and these types of arthritis represents one of the most important discoveries in the rheumatology field during the past five years.

Gastroenterology

Diseases of the gastrointestinal tract are associated with a high mortality (10 percent) and a significant morbidity. An estimated 3.4 million persons per year are hospitalized for a variety of digestive diseases and about 13 million Americans are affected by chronic digestive conditions. Gastroenterology research in the VA hospital system has been growing both in scope and in quality. It has emphasized investigation of the patho-physiologic basis for gastrointestinal disorders, of new

techniques for diagnosis and management and of prevention and treatment.

Esophagus and stomach

The lower esophageal sphincter largely determines how much gastric acid refluxes into the esophagus. A continuous reflux of gastric acid due to an incompetent sphincter is associated with inflammation of the esophagus which eventually may lead to a stricture. Important advances were made at the VA hospital (Wadsworth), Los Angeles, Calif. Gastric alkalinization did not cause an elevation of gastrin nor an increased sphincter pressure. These investigators confirmed the decrease of lower esophageal sphincter pressure by intestinal hormones such as cholecystokinin in pharmacological doses raising the question of whether gastrin and cholecystokinin regulate lower esophageal sphincter pressure under physiological circumstances. Investigators from the West Haven, Conn. VA Hospital have provided good evidence that a surgical approach (anterior fundoplication) for the treatment of reflux is effective since it restores the sphincter function to normal. Two drugs, Bethanecal and Metoclopramide, produced a significant increase in sphincter pressure with improvement in the symptoms of reflux without significant side effects. These new therapeutic approaches will influence the management of this common clinical problem.

Productive studies of the factors responsible for gastric acid secretion and gastric propulsion are being conducted at the Wadsworth VA Hospital. These factors may be related to the pathogenesis of duodenal and gastric ulcers. Gastrin, a known stimulator of gastric acid secretion, is secreted by the specific cells in the antrum of the stomach and duodenum but its role in the pathogenesis of duodenal ulcer has not been established.

Investigators at Wadsworth have demonstrated that patients with duodenal ulcer not only secrete more acid in response to stimulation by pentagastrin but also are more sensitive to gastrin; that is, they need smaller doses of pentagastrin to achieve the same fraction of the maximal response.

Also, at the same hospital, investigators have shown that gastrins with a different number of amino acid residues differ in their ability to stimulate gastric acid secretion. Separation of various gastrins could shed more light on the role of these hormones in the regulation of gastric acid secretion in normal subjects and in patients with duodenal ulcer.

Therapeutic trials of new drugs for treatment of the duodenal ulcer are now being conducted at Wadsworth and several other VA hospitals. H2 receptor blockers (Cimetidine, Metiamide) are useful in suppressing gastric acid secretion in gastrin producing tumors (Zollinger-Ellison Syndrome). Barring serious side effects, these may become therapeutic agents. In addition, investigators at Wadsworth are studying the possible therapeutic role of prostaglandin and secretin in the treatment of duodenal ulcer.

Investigators at the VA Hospital, Salt Lake City, Utah, reported that prostaglandin, a known inhibitor of gastric acid secretion, is not decreased in patients with duodenal ulcer. Consequently, its deficiency probably is not a cause of duodenal ulcer.

Progress was also made in understanding factors regulating gastric emptying. VA investigators at Iowa City, Ia., have demonstrated the important role of the first part of the duodenum in the control of gastric acid secretion and gastric emptying. Cholecystokinin, a small intestinal hormone, also inhibits gastric emptying as its physiologic function.

Studies to elucidate the pathogenesis of gastric ulcer include testing the hypothesis that bile salts can break the gastric mucosal barrier at the VA Hospital, West Roxbury, Mass. The high acidity of gastric juice augments the damaging effects of bile salts but the bile salt binding agent, cholestyramine, failed to prevent the toxic effects of bile salts on the gastric mucosa.

Upper intestinal hemorrhage is frequently life-threatening. Investigators at the VA Hospital, New Haven, Conn., have shown that the intra-arterial administration of vasopressin does not improve survival and does not significantly decrease the necessity for surgical intervention.

Pancreas and the biliary tract

Diseases of the pancreas and biliary tract are one of the most common disorders encountered in VA hospitals. Investigators at the VA Hosptial, Augusta, Ga., continued to provide information concerning transport, synthesis and secretion of pancreatic digestive protein in response to various gastrointestinal hormones. Several clinical, controlled trials at Wadsworth, Los Angeles, and Richmond, Va., VA Hospitals on the medical treatment of acute pancreatitis will greatly assist physicians in treating this common disease.

Investigators at the Richmond VA Hospital continued to study the hepatocellular regulation of bile salts, phospholipid and cholesterol metabolism in man and in experimental animals. The sensitivity and specificity of factors that control bile acid and cholesterol synthesis are being defined *in man*. These investigators have provided information about the role of bile salts in the transport of phospholipid and cholesterol from the site of synthesis into the liver and bile. Understanding of the mechanism regulating hepatic lipid synthesis and transport may lead to a better understanding of diseases of lipid metabolism including cholesterol gallstones, hyperlipidemia and arteriosclerosis. Investigators from Denver, Colo. and Richmond, Va., VA Hospitals have further defined the metabolic abnormality of secondary bile acid metabolism in patients with cirrhosis.

Selective biliary obstruction may prove to be an important model for the study of lipid metabolism in cholestasis. Investigators at the VA Hospital, Syracuse, N.Y., demonstrated that the administration of B–glycerophosphate to human subjects greatly increases the solubility of cholesterol in bile and this agent may prove to dissolve cholesterol gallstones. A thorough study in an unselected group of 100 paents with gallstones at the VA Hospital, Philadelphia, Pa., showed a higher incidence of pigmented stones than previously reported.

Progress is being made in diagnosing pancreato-biliary diseases by the use of endoscopic cholangiography and pancreatography. Gastroenterologists at the VA Hospital, Minneapolis, Minnesota, have contributed to the development and improvement of these techniques.

Liver

Many VA investigators are interested in liver disease. Research at the Bronx, N.Y. VA Hospital has contributed to the understanding of basic mechanisms of alcohol degradation and the toxic effects of alcohol on the metabolism of protein, carbohydrates, and fat, and has related these changes to clinical problems. The Bronx investigators have developed an experimental model of chronic alcoholism in baboons and used it to study the natural history of alcoholic injury. In these studies the animals developed fatty liver, alcoholic hepatitis and cirrhosis in spite of maintenance of an adequate diet. These investigators also observed that the serum acetaldehyde, a degradation product of alcohol is higher in alcoholic subjects than non-alcoholics. Numerous toxic effects have been attributed to this compound, including mitochondrial damage, inhibition of oxidative phosphorylation, and decreased synthesis of myocardial protein.

VA hospitals have tested several measures to improve the prognosis of chronic liver disease and its complications. The controlled study of portocaval shunt for gastrointestinal bleeding secondary to cirrhosis showed no significant differences in survival between different types of shunts.

More discouraging was the fact that no operation was significantly better than medical management. At the VA Hospital, West Haven, Conn., a controlled trial of chronic hepatic encephalopathy, a common complication of acute and chronic liver disease, demonstrated that a synthetic disacharide (Lactulose) is as effective in the treatment of these disorders as non-absorbable antibiotics. Prolonged use of non-absorbable antibiotics may cause kidney toxicity. Similarly, lactose can be useful in the treatment of hepatic encephalopathy in patients with a lactase deficiency.

VA investigators at West Haven and Wadsworth have demonstrated the frequent existence of bacterial peritonitis during cirrhosis. Early recognition of this complication results in a better prognosis. Investigators at the VA Hospital, Syracuse, N.Y., reported that cirrhotic patients have impaired absorption of micellar long-chain fatty acids, possibly related to portal or lymphatic hypertension contributing to maldigestion and malabsorption. It was reported from the Bronx, N.Y. VA Hospital that acute ethanol administration enhances intestinal lymph formation and fat transport. In contrast, chronic intake of alcohol inhibits these effects, establishing the direct toxicity of ethanol on the gut.

Investigators at the VA Hospital, Nashville, Tenn., are studying the effect of liver disease on the disposition and elimination of a variety of drugs. The elimination of Meperidine, Paraldehyde, Phenobarbital and Diazepam in cirrhosis is slow because the drug metabolizing activity of the liver is impaired. These drugs should be used cautiously in patients with liver disease since they may precipitate hepatic coma. Another tranquilizer, Oxazepam, is eliminated normally in patients wtih liver disease and should provide a greater margin of safety.

Investigators at the VA Hospital, New York, N.Y., have observed that alcohol depresses albumin synthesis by the liver and causes marked disaggregation of the endoplasmic membrane bound polysome, an

effect which can be reversed by certain amino acids. These studies indicate another toxic effect of acute and chronic alcohol intake.

Small intestine and large colon

Investigation of the small intestine was oriented mainly towards the physiological processes involved in the digestion of food and vitamins, including lactose intolerance which is a common clinical problem. Intolerance to milk is particularly high among blacks (in excess of 70 percent).

Investigators at the VA Hospital, Madison, Wis., have demonstrated that in children with T-cell deficiency, the presence of diarrhia and malabsorption is associated with histological features similar to that of Whipple's disease suggesting the possibility of defective host defense. The importance of oral lactose and sucrose tolerance tests as well as small intestinal histology in diagnosing chronic diarrhia in children has been demonstrated from the studies at the VA Hospital, Oklahoma City, Okla. VA investigators at San Francisco have elucidated various phases of protein absorption. At the VA Hospital, New York, N.Y., it was shown that sodium taurochenodeoxycholate, as opposed to taurocholate, does not enhance cholesterol absorption. Chenodeoxycholic acid may be used in the near future as a medical therapy for dissolution of cholesterol gallstones in man. Inhibition of water absorption and reduced circular smooth muscle activity are probably the factors responsible for castor-oil and magnesium sulfate-induced catharsis, according to studies at the Madison VA Hospital. The mechanism of thiamine (B_1 vitamin) absorption has been elucidated by the investigators at the VA Hospital, Nashville, Tenn.

In recent years small intestinal hormones have proved important in regulating gastric acid and pancreatic excretion, motor activity of the gut and absorption. VA Hospital investigators at Dallas, Texas and Wadsworth, Los Angeles, have contributed significantly to studies on the physiologic roles of secretin, gastrin, cholecystokinin, glucagon, and other "candidate hormones" which are being continuously evaluated in several VA hospitals.

Hematology and sickle cell disease

Anemias, hemoglobin and sickle cell anemia

Several new mutations of hemoglobin have been identified by VA investigators. Hemoglobin Grady, a fast-migrating hemoglobin mutation of the α chain, was identified by researchers at the VA Hospital, Augusta, Ga. This mutation involves the insertion of three additional amino acids into the chain. These three amino acids are repeated in the adjacent sequence, suggesting that their duplication resulted from mismatched intragenic crossing-over. This is the first report of this type of mutation in hemoglobin.

A new unstable hemoglobin variant, hemoglobin Ann Arbor, was discovered at the VA Hospital, Chicago (WS), Ill. Its presence resulted in a hemolytic anemia. The mutant α chain is so unstable that it is rapidly destroyed and leads to the unbalanced production of normal α and β chains. A patient with two mutant hemoglobins, Hope and Sickle, was studied at the VA Hospital, Jackson, Miss. Hemoglobin

Hope is unstable and, in combination with hemoglobin S, produces only a mild hemolytic anemia, much less severe than any of the recognized common sickling disorders.

In a continuation of previous work, VA investigators at Augusta, Ga., have published comparative studies on the variants that have been described in the minor adult hemoglobin A_2. The same laboratory has added to our understanding of the heterogeneity of human fetal hemoglobin in thalassemia and other related disorders.

Investigators at the VA Hospital, Dayton, Ohio, described the occurrence of multiple pulmonary emboli in a patient with hepatic cirrhosis, portal hypertension and sickle cell trait. At autopsy the emboli were composed of sickled cells. Alcoholism may have contributed to the sickling but sickle trait is so prevalent that its occurrence with other rare clinical events may result merely from chance. Sickle cell trait is usually considered a benign condition.

Zinc deficiency associated with delayed maturation was described in patients with sickle cell anemia by investigators at the VA Hospital, Allen Park, Mich. Five male adolescents responded to oral zinc therapy with evidence of sexual maturation; two increased significantly in height. The investigators are now determining whether zinc supplementation decreases the incidence of painful crises in persons with sickle cell anemia.

The double-blind clinical trial of oral sodium cyanate has been completed at the VA Hospital, Miami, Fla. Most patients had impressively prolonged red blood cell survival and increased hemoglobin levels while taking cyanate. The incidence of painful crises did not, however, decrease and significant toxicity was observed. Of 19 patients who completed the study, 7 had weight loss exceeding 5 percent. 4 showed evidence of subclinical neuropathy which is reversible when the drug is stopped, and one patient developed cataracts. Orally administered cyanate was deemed unsafe and ineffective as treatment of sickle cell anemia.

A new antisickling agent is being studied at the VA Hospital, San Francisco, Calif. This chemical, dimethyl adipimidate, completely inhibits sickling and makes several properties of the treated sickle cell more nearly normal. It is one of a class of chemicals which interact with proteins and cross-link two or more molecules. Studies of this potentially useful compound are continuing in several collaborating laboratories.

Investigators from the VA Hospital, Northport, N.Y., described a remission with immunosuppressive drugs in a patient who had a production defect of red blood cells caused by a circulating antibody to red cell precursors. This is the fourth case of autoimmune pure red cell aplasia successfully treated in this manner. The three previously described cases were studied by VA investigators at Nashville, Tenn. The latter published the most extensive recent review of current knowledge regarding erythropoietin, the hormone which regulates red blood cell production.

At the VA Center, Los Angeles (Wadsworth), Calif., researchers investigated a patient with hereditary hemolytic anemia caused by a previously unrecognizable variant of the red cell enzyme glycosephosphate isomerase. The same laboratory reported a form of hereditary

anemia resulting from an abnormality of the enzyme pyrimidine 5′-nucleotidase in the patient's erythrocytes, and has defined the underlying problem of more types of hereditary hemolytic anemias due to enzyme abnormalities than any other laboratory in the world.

An animal model was developed for the hemolytic anemia and bleeding disorder associated with clinical hyperalimentation at the VA Hospital, Minneapolis, Minn. Infusion of amino acids and glucose rapidly produced the clinical syndrome. A severe depression in serum phosphate led to secondary effects on the metabolism in red cells and platelets which resulted in a fall at ATP. The red cell survival and platelet function could be returned to normal by adding inorganic phosphate to the infusion mixture. In patients receiving hyperalimentation, impaired central nervous function and defective leukocyte function have also been described and may be due to the same metabolic derangement from phosphate depletion.

At the VA Hospital, Chicago (WS), Ill., studies of both animals and man have revealed large numbers of peripheral blood cells which are able to form new colonies of cells in culture. Nearly 80 percent of the cells retain this capacity after cryopreservation for 30 days. Stored peripheral white blood cells promptly repopulated the marrow after supralethal irradiation in animals. Thus peripheral blood may be potentially useful for marrow grafting purposes.

Hydroxyethyl starch has been studied as a cryoprotective agent in frozen-thawed blood in monkeys at the VA Hospital, Ann Arbor, Mich. This protective agent need not be separated from the blood prior to its transfusion; other agents such as DMSO and glycerol, must be removed. The frozen blood protected monkeys against shock and caused no bleeding problems. Previous reports indicated that hydroxyethyl starch caused platelet clumping and coagulation abnormalities but no pathological changes due to the hydroxyethyl starch could be identified at autopsy. This type of cryoprotective agent would save time and money if it can be proved safe.

Vitamin B_{12} and pernicious anemia

At VA Hospital, Albany, N.Y., improved methods have been developed for measuring several different plasma vitamin B_{12} binding proteins. The techniques may differentiate closely related blood disorders, such as polycythemia vera and chronic myelocytic leukemia, in which different types of vitamin B_{12} binding proteins are elevated. Studies of blood eosinophils (cells which are increased in allergic, parasitic, and skin diseases) in mice at the VA Hospital, Nashville, Tenn., have revealed that there is great diurnal variation in their circulating numbers. At midday the eosinophil count is maximal and it is minimal around midnight. Removing blood from animals markedly increased the circulating eosinophils for nearly 24 hours. Little is known about the regulation of eosinophils proliferation but this work is now being extended to man.

Investigators at the VA Los Angeles (Wadsworth) Calif. Center using highly sensitive immunologic techniques demonstrated that nearly all patients with pernicious anemia have evidence of cellular immunity against hog stomach intrinsic factor. Previous studies have shown that circulating antibodies to intrinsic factor and to stomach cells are present in at least some patients with pernicious anemia.

Whether this altered immunity causes the disease or results from it is unknown but patients with other abnormalities of the gastrointestinal tract do not possess the antibodies.

Bleeding disorders, platelets and blood coagulation

Investigators at the VA Hospital, Durham, N.C., developed a method to detect and measure antibodies on the surface of blood platelets. This assay confirmed the diagnosis of idiopathic autoimmune thrombocytopenic purpura. Patients with greater quantities of antibody on their platelets were refractory to adrenal steroid therapy.

At the VA Hospital, Bronx, N.Y., a patient was studied with immune thrombocytopenic purpura resulting from aspirin ingestion. Though ingestion of aspirin is frequently associated with clinical bleeding this is only the third time that such bleeding has been ascribed to an immune basis. VA investigators in Madison, Wis., reported on a patient with immune thrombocytopenia associated with ingestion of chloropheniramine, an antihistamine. This is the first report of thrombocytopenia due to this drug and only the second case described as drug-induced immune thrombocytopenia associated with any frequently used antihistamine.

At the VA Hospital, Miami, Fla., a patient who bled extensively after an operation had been taking clofibrate. Xylocaine was used as the local anesthetic. These two drugs were profoundly synergistic in blocking platelet aggregation induced by collagen patients or normal volunteers.

The pathogensis of bleeding in von Willebrandt's disease, a hereditary bleeding disorder, is complex and incompletely understood. Investigators at the White River Junction, Vt. VA Hospital, found that patients with this disorder have fibroblasts which, grown in tissue culture, are deficient in tissue factor, a coagulation factor. This factor is employed in routine laboratory assays of coagulation. Fibroblasts from normal persons or persons with other known hereditary bleeding disorders had normal tissue factor activity.

Leukocytes are known to be a source of the tissue factor. When endotoxin, a product of certain types of bacteria, interacts with leukocytes tissue factor is produced. The presence of platelets, platelet membranes or granules prepared from platelets stimulates tissue factor release from white blood cells by endotoxin. VA investigators at the VA Hospital, Bronx, N.Y., suggested that in sepsis these three factors (leukocytes, platelets and endotoxin) cause the disseminated intravascular coagulation that frequently contributes to the death of these patients.

Patients requiring surgery may have an inability to control bleeding discovered through preoperative tests of bleeding time and platelet count. Normally platelets release a blood-clotting substance and themselves help close any vascular opening through which blood escapes. A platelet transfusion in which only the blood type of the donor is matched with that of the recipient often fails to stop the bleeding because the platelets are rapidly destroyed by antibodies in the recipient. Platelet transfusions from brothers and sisters suggested that histocompatibility was the problem. The body's immune system will destroy, if possible, any tissue or particle which does not have an inherited pattern. This individual pattern includes a major locus of

antigens—Histocompatibility Locus A (HL–A) and other minor loci. For platelet transfusions, the VA investigators at the Chicago (Res.), Ill., VA Hospital found that when the HL–A of donor and recipient match platelets survived longer in the recipient and more effectively prevented bleeding during and after surgery. The investigators used available relatives to obtain HL–A matches; otherwise, computer-assisted-determinations selected matched donors from volunteers among the hospital personnel.

Immunology

Immunologic aspects of connective tissue diseases

Two connective tissue diseases under study are systemic lupus erythematosus (SLE) and Sjögren's syndrome. Research at the Dallas, Texas, VA Hospital has shown that the deposition of immunglobulin at the dermal-epidermal junction of human skin correlated well with the deposition of immunoglobulins in the glomerulus of the kidney.

During the past year these findings have also been demonstrated in hybrid mice, a rather striking model of human SLE. Demonstration of this finding should permit further analysis of the phenomenon to determine its prognostic and clinical significance. At the Denver, Colo., VA Hospital, specific removal of antibody to DNA with an insoluble DNA-cellulose immunoabsorbent was achieved in an *in vitro* system which could be adapted for *in vivo* extracorporeal removal of such antibodies. The DNA-antiDNA system is the most important type of immune complex contributing to serious renal disease in SLE.

At the Buffalo, N.Y., VA Hospital, a new RNAprotein antigen of cytoplasmic origin was found to react specifically with antibodies in the sera of patients with SLE and also in the sera of patients with Sjögren's syndrome (25 percent). A few patients with such antibodies to cytoplasmic RNAprotein, but without antinuclear factors, have the clinical picture of SLE. They may represent part of the spectrum of SLE overlooked because they lack antinuclear antibodies throughout their course.

At the San Francisco, Calif., VA Hospital, B2 microglobulin, a small polypeptide which is a part of membrane of peripheral blood lymphocytes, was increased in the saliva of patients with Sjögren's syndrome and in the synovial fluid of patients with rheumatoid arthritis. The level of B2 microglobulin in the saliva seems to correlate with the level of disease activity and might guide therapy. There are no other laboratory parameters at present that correlate with disease activity and a search for viruses in labial biopsy specimens from Sjögren's patients yielded no positive results.

Immunological aspects of pulmonary disease

Also at the San Francisco VA Hospital, basic studies are underway to characterize the immunological features of immune responses in the lungs. An animal model was developed and the lymphocytes in the respiratory tract have been characterized and compared to systemic lymphocytes. Immunization by aerosol was compared to systemic immunization and the relative distribution of sensitized cells after ex-

posure by the two routes has been ascertained. These studies show that the lung is immunologically active, has specific features in terms of the kinds of cells generated (1gM and 1gG but not 1gA cells to sheep erythrocytes), can participate in immunization in a primary fashion and can maintain specific functional characteristics.

At the Wood, Wisc., VA Hospital, there have been studies of various types of hypersensitivity pneumonitis, including Pigeon breeders disease. This inflammatory lung disease seems to have two components: one, an immune complex disorder and the second, a cell mediated process with both antibody and cells directed toward pigeon serum proteins and other avian proteins. Techniques for the assessing of precipitins and cell-mediated responses to these antigens have been developed and refined to support this interpretation.

A case of allergic pulmonary aspergillosis has been studied and the report suggests that this disease, which is not rare in Great Britain, may be a problem in the USA.

An epidemiologic study relates hypersensitivity peneumonitis to thermophilic fungi. More of such organisms can be cultured from the homes of patients and more patients than controls have precipitating antibodies to antigens from the organism. Finally, patients with inflammatory pulmonary disease which developed during treatment with nitrofurantin provided evidence for lymphocyte reactivity against nitrofurantin. Cellular hypersensitivity to nitrofurantin may play some role in the pathogenesis of pulmonary inflammatory disease.

Immunological aspects of malignancy

Animal models of malignancy have been studied with respect to specific immunological features. At the Sepulveda, Calif., VA Hospital, murine fibrosarcomas were treated by immunization with BCG, a tuberculosis-like organism which is known to enhance cell-mediated immunity and/or neuraminidase, an enzyme which removes sialic acid from molecules bearing it. Some regimens could enhance growth or cause regression depending on the specific tumor and the timing of the therapy. At the San Francisco, Calif., VA Hospital, it was shown, using alloantibodies against murine EL-4 lymphoma and P-815 mastocytoma cells, that cytotoxic complement-fixing antibodies could be converted to blocking antibodies by lysozomal enzymes from the tumors themselves. Such effects in vivo could contribute to enhanced tumor growth.

A report from the Chicago (WS) Ill., VA Hospital illustrates how cells can be recruited into a malignant clone by means of its surface immunoglobulin, a mechanism not requiring cell division. In the plasmacytoma system, RNA extracts from tumor cells can cause the appearance of plasmacytoma 1g on the surface of normal lymphocytes. At the San Francisco VA Hospital, lymphomas which arise in hybrid mice have been characterized as B cell tumors. Such lymphomas arise in one-third of the mice who survive longer than 12 months.

Basic Investigations of immunochemistry, complement, and all mediated mechanisms

At the VA Hospital, Iowa City, Ia., specific antibodies, purified by isolectric focusing techniques and the ability of fragments of such antibodies to bind antigen, is under investigation. At the Wood, Wisc.,

VA Hospital, studies suggest that the alternate pathway of complement activation plays a role in releasing histamine from the leukocytes of allergic individuals. Studies at the Nashville, Tenn., VA Hospital, show that the alternate pathway can induce platelet aggregation, a phenomenon which may underlie certain inflammatory reactions. At the Houston, Texas, VA Hospital, research is in progress on the regulation of cell-mediated immune responses and the short-term effects of corticosteroids on immunoglobulin synthesis. At Nashville a substance released from lymphocytes which promotes the appearance of eosinophiles has been partially characterized. At the VA Hospital, Buffalo, N.Y., research on the characteristics of antibodies that distinguish single amino acid differences in proteins reveal them to be quite homogeneous, resembling myeloma proteins.

Infectious diseases

A broad, intensive research program in infectious diseases continues in the VA involving most hospitals in the system and contributing significantly to better patient care. This type of investigation bears on such other medical problems as cancer, heart disease, emphysema, collagen diseases, complications of narcotic usage and infections in travelers. In addition to its clinical application, it advances knowledge in basic fields such as microbiology and immunology.

Bacterial infections

A cooperative study reported this past year analyzed data on 89 strains of slow-growing organisms related to the tubercle bacillus using a numerical taxonomic method. Five distinct species were recognized. The international research group embraced 18 institutions including the VA Hospital, Long Beach, Calif. A group at the VA Hospital, Wood, Wisc., is studying glycoprotein biosynthesis in another type of mycobacterium. The morphology of a bacterial virus (bacteriophage) active against still another mycobacterium was studied by investigators at the VA Hospital, Little Rock, Ark.

At VA Wadsworth Hospital Center, Los Angeles, Calif., investigators found that anaerobic bacteria vary greatly in their sensitivity to oxygen, some tolerating as much as 10 percent oxygen in the atmosphere and others requiring 0.4 percent or less. Survival in air, between transfers, was relatively long indicating that simplified procedures may be effective in culturing these bacteria from patients.

Investigators at the VA Hospital, Iowa City, Iowa, studied the metabolism of a type of Pseudomonas, sometimes found in infections, which is able to grow at 0° C. One critical enzyme in this organism is active at very low temperatures.

So-called L forms of bacteria, which have no or deficient cell walls have been suspected of being responsible for the chronicity of certain infections; exacerbations may relate to reversion to the original bacterial form. While the sigificance of this phenomenon in human disease remains uncertain, work done in collaboration with the VA Hospital, New Orleans, La., demonstrated that the process of microbial persistence as L forms and the reversion can take place in human embryonic kidney cells in tissue culture. Several VA facilities—Iowa City, Sepulveda, Chicago, and Long Beach, have investigated the mechanisms of diarrhea production in various dysenteries or diarrheal states.

Enhanced small intestinal loss of fluid and electrolytes is mediated by the adenyl cyclase-cyclic AMP system in cholera and in toxigenic *E. coli* diarrhea, an important type of travelers diarrhea and a cause of other forms of gastroenteritis in adults and babies, the mechanism was demonstrated in various test systems including tissue cultures of adrenal tumor cells.

The toxins elevate intracellular levels of cyclic AMP in virtually all mammalian tissues and are therefore potentially valuable tools for studying the molecular events of all related cellular phenomena. These include the effects of hormones at the cellular level, cell growth and division, and the relationship between prostaglandin and adenylate cyclase. A surface-active antibiotic, polymyxin, has been utilized to release from *E. coli* a certain type of diarrhea-producing toxin so that it can be better characterized.

Antibodies can be produced against at least one type of toxin produced by *E. coli* and these cross-react with cholera toxin. Toxin assay procedures permit serologic types of epidemiologic investigations and the evalaution of vaccines or toxoids. Other types of diarrhea-related toxins, namely those produced by the dysentery bacillus and by *Clostridium perfringens* which causes food-poisoning apparently have a mechanism of action which differs from the toxins.

A clinical study by a group of VA investigators from Sepulveda, Calif., documents the frequency with which toxin-producing strains of *E. coli* may cause traveler's diarrhea, a poorly understood entity. About 70 percent of such illness in a group of U.S. students traveling in Mexico was associated with these *E. Coli.*

The pneumococcus, a type of streptococcus, is still an important cause of pneumonia, especially among the aged. The organisms may, in the course of pneumonia, cause bacteremia or blood-poisoning and other serious complications so that this illness has a mortality of 28 percent despite effective antibiotics, according to work done at the VA Hospital, Chicago (WS), Ill.

VA investigators are active in the area of bacteriologic diagnostic techniques in infectious disease practice. At VA Hospital, Long Beach, Calif., as part of an International Working Group on Mycobacterial Taxonomy, investigators evaluated techniques for species identification in the complex group of organisms producing tuberculosis and related diseases; several were highly reproducible.

Investigators at VA Wadsworth Hospital Center, Los Angeles, Calif., have determined the validity of three subgroups of *Bacteroides melaninogenicus*, have compared three procedures for biochemical testing of anaerobic bacteria and have found simple procedures to be suitable for identification. They have summarized the use of gas chromatography for the detection and identification of anaerobic bacteria. At Sepulveda, Calif., VA researchers have used gas chromatography for presumptive detection of botulism-causing organisms in spoiled food.

A VA group at Wadsworth has developed and evaluated a membrane filter procedure for the rapid detection and identification of bacteria in the blood stream. This offers promise of permitting earlier and more effective therapy in blood-poisoning, still one of the most serious of infectious diseases. The value and pitfalls of certain blood tests for antibody detection and of skin tests in the diagnosis

of infections have been evaluated by VA researchers at Richmond, Va., and at Albuquerque, N. Mex.

Clinical studies of infectious diseases in the VA system have involved collaboration between the groups at Sepulveda and Wadsworth Hospital Center, Calif. They documented the role of anaerobic bacteria in a variety of pulmonary infections including aspiration pneumonia, lung abscess, empyema and others. They stress the special techniques required to avoid overlooking these important pathogens since many infections have been attributed to other organisms and therapy has not uncommonly been misdirected as a result. Other workers at Wadsworth studied the role of anaerobic bacteria in neonatal bacteremia and in subdural empyema.

At Oklahoma City, Okla., VA workers, in collaboration with Vietnamese investigators, detected significant (46 percent) resistance of typhoid bacilli to chloramphenicol, formerly the drug of choice, in Saigon and determined that ampicillin and cotrimoxazole were satisfactory alternatives.

Infections due to microorganisms other than bacteria

So-called "slow viruses" produce several chronic neurologic diseases in animals and such organisms may cause similar human diseases. A VA group at San Francisco, Calif., has been involved in a series of basic investigations of such viruses involving analysis of their structural polypeptides, comparison of RNA with that from a tumor virus and, investigation of the mechanism of nucleic acid synthesis and study of its products.

Fundamental studies of a natural infection with two different viruses in single cells in a tissue culture line have been reported from the VA Hospital, West Haven, Conn. Latent herpes virus was recovered from the spinal ganglia of mice without illness by VA investigators at Chicago (WS), Ill. In young adults this prevented clinical illness due to one of the common cold viruses by means of a topical interferon inducer administered as nose drops for two days, beginning one day before challenge with the virus. Other investigators at the same VA facility found evidence that certain adenoviruses play a role in some cases of acute hemorrhagic cystitis and detected the presence of one of the viruses causing infectious hepatitis among natives in remote parts of Africa.

Parasitic infestations continue to attract the interest of VA clinicians and researchers. An investigation of the effect of chloroquine on the maturation of certain malarial parasites in man was reported from the VA Hospital, Iowa City, Iowa.

A VA investigator at New Orleans, La., has confirmed that counterimmunoelectrophoresis can be utilized in a relatively rapid, dependable serologic test for amebiasis. A serologic test for the diagnosis of visceral larva migrans, a serious worm infestation, has been described as well as evidence for a parasitic fluke infection in prehistoric man.

VA investigators at Long Beach, Calif. contributed to the standardization of reagents and methods in medical mycology. Infectious particles called xenosomes were reported to occur in unicellular animals. These self-replicating particles, a single one of which is infectious to certain salt water protozoa, are larger than viruses, contain large amounts of DNA and are unique in that they contain multiple copies of complete genetic information.

Host defense mechanisms against infection

Much attention is being given to host defense mechanisms in infectious diseases. Cell-mediated immunity in relation to various viral infections is under investigation at VA Hospitals in Houston, Texas, Cincinnati, Ohio, and Brockton, Mass. In infectious mononucleosis, cutaneous energy may occur along with hypo-responsiveness of lymphocytes or macrophage precursors in the blood and with transient but marked decrease in the number of white blood cells.

In rubella infection, skin hypersensitivity was markedly impaired at the height of the illness but lymphocyte function was otherwise normal. Mild viral respiratory infections, however, had no influence at all on cell-mediated immunity. An *in vitro* assay of cell-mediated immunity to measles virus was described, permitting an explanation of abnormal host reactivity which may predispose to subacute sclerosing panencephalitis.

Bacteroides fragilis is the most commonly encountered anaerobic pathogen. The most common subspecies in clinical infection were shown by investigators at Wadsworth Hospital Center, Los Angeles, Calif., to be resistant to normal serum factors which kill strains of fecal flora. Phagocytosis and killing of anaerobic bacteria by human leukocytes was also noted. Estrogens have been reported to enhance phagocytic activity in animals.

At the VA Hospital, Oklahoma City, Okla., estrogen administered orally to patients with meningitis due to cryptococcus resulted in moderate to marked stimulation of phagocytosis and disappearance of circulating capsular material from the fungus.

VA investigators at Pittsburgh, Pa., demonstrated that antigen stimulation of leukocytes enhances release of a prostaglandin. Further work must determine the mechanism of this phenomenon and its biologic significance.

Therapy and prophylaxis

A standardized procedure for determining suspectibility of slow-growing anaerobes to antimicrobial agents by the simple disc technique was described. VA investigators at Wadsworth and Sepulveda, Calif., have reported independently and jointly on the suspectibility of anaerobic bacteria to various penicillins and cephalosporins and on the susceptibility to various antimicrobial agents of *Clostridium ramosum*, a common but often overlooked pathogen.

A pharmacologic and clinical investigation of intramuscular and intrathecal gentamicin for meningitis due to Gram-negative bacilli was reported by investigators at the VA Hospital, New York, N.Y. In experimental murine coccidioidomycosis, tetracycline administered with amphotericin significantly reduced the amount of more toxic agent required for a good response. Protective immunity against amebiasis was produced in guinea pigs by a researcher at the VA Hospital, New Orleans, La.

Allergy

Studies on asthma in spontaneously ragweed-sensitive animals and its response to prednisone were reported from Wood, Wis., VA Hospital. The steroid completely prevented the asthma during and for three months after cessation of treatment. Clinical studies of alpha and beta adrenergic imbalance in intrinsic intolerance rhinitis and

asthma were carried out at the VA Hospital, Chicago (WS), Ill. The same workers studied the risks of using aspirin as an anti-hemostatic agent in hypersensitive patients and proposed a method to reduce the risks. Studies of immunologic tolerance in animals have been reported and a role for regional lymph nodes in tolerance production is postulated.

Mental health and behavioral sciences

Psychotherapy is the most expensive treatment employed with psychiatric patients. Yet its efficacy is uncertain, the specific effects of different techniques remains unknown and the best way to select particular treatments is undetermined. VA investigators attack these problems employing controlled methods of evaluation.

Kind-firmness attitude therapy as a treatment for depression consists of prolonged, ungratifying work designed to prod the patient toward assertive expressions of anger, thus relieving the depression. A research team at the VA Hospital, Tuscaloosa, Alabama, compared kind-firmness and conventional therapy employing active friendliness and anti-depressant medication. Both treatments reduced anxiety about equally well among neurotics but kind-firmness was more effective in alleviating depression. Psychotics treated with this approach showed significant reduction in tension but no decrease in anxiety-proneness while psychotics treated on the conventional program demonstrated the opposite pattern.

Another radical treatment, implosive therapy, requires the patient to imagine his worst fears in an exaggerated state so that he can realize their irrationality and rid himself of them. An investigator at the VA Hospital, Iowa City, Iowa, compared the five-year rehospitalization rates of patients randomly assigned to implosive therapy and traditional milieu treatment. The former had a significantly lower rehospitalization rate over that period.

Another unconventional treatment uses volunteers to serve as "big brothers" to chronic patients leaving psychiatric hospitals. A VA controlled study at Bedford, Mass., Tuscaloosa, Ala., Marion, Ind. and St. Cloud, Minn., compared the progress of patients released on such a program to that of a group not assigned to volunteers. The two groups had the same amount of change on a wide variety of adjustment and recidivism measures during the ensuing 12 months. The outpatient volunteers did not help psychiatric patients and the program was discontinued.

Depression is a particularly common psychiatric problem endangering society's mental health and its economic well-being. Researchers in 18 hospitals cooperated in comparing the prophylactic effectiveness of the two major anti-depressant drugs—lithium carbonate and imipramine—in discharged patients. Both drugs prevented relapse when compared to placebo treatment. Unipolar depressives responded equally well to both drugs; manic-depressives improved more with lithium.

VA investigators also made substantial progress on psychological testing problems this year. At St. Cloud, Minn., four studies compared the abilities of 15 short intelligence tests to predict Wechsler Adult

Intelligence Scale scores. Most institutions rely on short group intelligence tests rather than the better but lengthier and more costly Wechsler Adult Intelligence Scales. The VA research provides the first comprehensive comparison of short tests to the Wechsler scales. Two short tests—the Henmon-Nelson and the Test of Educational Ability—were significantly better than most of the more familiar, commonly used ones.

Most psychological brain-damage tests cannot separate brain-damaged persons from other psychiatric patients. This has caused functional psychiatric patients to be misdiagnosed as brain-damaged and has led VA investigators to develop a scale derived from the Minnesota Multiphasic Personality Inventory for separating brain-damaged from schizophrenic groups. During the past year, VA investigators at Brecksville, Ohio and Topeka, Kansas have verified this scale's ability to make the separation.

The Brecksville group also provided evidence that the Minnesota-Precepto Diagnostic test, a copying task, may distinguish organic brain damage from schizophrenia if administered on special "Background Interference" paper. The paper resembles an assembled jigsaw puzzle and tends to interfere with the performance of brain-damaged patients more than with that of schizophrenics.

Neither the causes nor the precise nature of the cognitive deficits in major psychiatric illnesses are well understood. One theory of schizophrenia maintains that the pathological symptoms represent little more than attempts to obtain financial benefits and a non-demanding environment by appearing helpless. A VA study, however, indicates that schizophrenics actually have *less* ability to manage the impressions they make on others than do other psychiatric and non-psychiatric groups. These results undermine the theory.

A team at the VA Hospital, San Diego, Calif., has developed a questionnaire to assess loss of remote memory based on the ability to recognize the names of past television programs, race horses and news events. With it the team has made the first controlled studies of the effects of electric shock therapy (ECT) on memory for remote events. Five ECTs will produce retrograde amnesia going back five to eight years but this amnesia is reduced by 50 percent within two weeks. In a study of remote memory under normal conditions, the number of memory traces decreased with time, but the resistance of the surviving traces to disruption hardened over the years. Very long-term memory was less often destroyed by ECT and traces older than 8 years persisted. Memories intact at that time were likely to last indefinitely.

Few non-invasive techniques can evaluate the brain activity of human subjects. One method involves averaging the electroencephalographic (EEG) activity as recorded from the scalp after repeated stimuli. The EEG activity which is unrelated to the stimulus varies randomly and its average tends toward zero; electrical potentials ("evoked responses") related to the stimuli remain evident and measurable. The responses elicited by auditory, visual and somatic stimuli have different distinctive characteristics.

One basic question is the effect of age on evoked responses. VA investigators at Salt Lake City, Utah, have described visual, auditory and somatosensory responses in 225 normal subjects between the ages

of 4 and 16 years and in an additional 200 subjects between the ages of 17 and 86 years. They demonstrated maturational changes in the younger groups and effects of aging in the older subjects. The changes with age were particularly prominent for visual stimuli and are the most pronounced age-related changes in any measure of waking brain activity investigated thus far. The Salt Lake City investigators have also pioneered in the application of evoked response techniques to patients with cerebral pathology, including those with Down's syndrome and centrencephalic epilepsy. They are currently assessing the value of responses as indicators of brain death.

Another non-invasive measure of brain activity is the sleep EEG which is also sensitive to age and to the effects of psychoactive drugs. A VA investigator in San Francisco, Calif., in collaboration with researchers at the University of California, found substantial effects of large doses of THC, the active ingredient of marijuana, on the sleep EEG. These are the most clear-cut effects of THC on human brain activity demonstrated thus far, but their significance is unknown.

VA investigators continue to contribute substantially to the basic and clinical understanding of drugs used in the treatment of major mental illnesses. VA investigators at Palo Alto, Calif., compared systematically the efficacy of 3 different chemical classes of anti-schizophrenic agents. They found no differences in the overall effectiveness in 320 newly-hospitalized schizophrenic patients although piperazines were somewhat more effective in older patients with core schizophrenic symptoms. The investigators concluded that differences in response to anti-schizophrenic drugs more likely reflect idiosyncratic differences in drug absorption or metabolism than major pharmacologic differences.

Lithium salts, widely used in the treament and prophylaxis of manic-depressive illness, were evaluated in a VA-NIMH collaborative study of prophylactic lithium therapy in 205 patients with bipolar manic-depressive illness. Lithium was superior to placebo for preventing new attacks. A poor response was associated with a recent history of frequent episodes of illness and with a previous failure of lithium therapy.

VA investigators in Philadelphia, Pa., investigated the effects of lithium on EEG sleep patterns of hospitalized depressed patients. Lithium reduced awakenings increasing stage 4 sleep while decreasing the duration of rapid eye movement sleep and the intensity of eye movements during this phase. The Philadelphia team studied the effects of two amino acid precursors, l-dopa and l-tryptophane, on depressive symptoms under double-blind conditions to evaluate the catecholamine hypothesis of affective disorders. There were no effects suggesting that the catecholamine hypothesis, at least in its simple form, is insufficient.

Nephrology

Prevention of kidney disease

Endogenous or exogenous compounds that may alter renal function or induce disease must be studied in animal models of human disease. VA investigators at Los Angeles, California developed a model of urate nephropathy by feeding oxonic acid, a known inhibitor of

uricase, to rats. Urate-blockade nephropathy results when the animals are fed oxonic acid for three weeks. One year's administration causes chronic interstitial nephritis resembling gouty nephropathy.

Employing a similar animal model investigators at the VA Hospital, Durham, N.C., decreased renal function within one week by giving oxonic acid alone or in combination with high uric acid feedings. The lesion may be due in part to precipitation of uric acid in the collecting ducts and seems more severe in the deeper nephrons and with the combined treatment.

VA investigators in Houston, Texas showed that intravenous mannitol protects renal function in renal transplant recipients who are given the nephrotoxic agent amphotericin B for systemic fungal infections. Bicarbonate given in addition to mannitol helps circumvent both postulated mechanisms of renal injury—the vascular effect and the cellular injury.

According to investigators at the VA Hospital, Iowa City, Iowa, decreased clearance of paraaminohippurate (PAH) may not in fact reflect decreased renal blood flow during anesthesia. Some general anesthetics, such as methoxyflurane, decease the transport of PAH in rabbit kidney slices.

Investigators at the VA Hospital, Palo Alto, Calif., studying the nephrotoxocity associated with anethestic agents have demonstrated that other general anesthetics (enflurane), which like methoxyfluorane are partially metabolized to fluoride, cause polyuria and vasopressin-resistant renal dysfunction in a special strain of rats. These animals break down fluorinated compounds in a fashion similar to man and the results have led to a clinical evaluation of fluorinated anesthetics.

Nephropathy in drug addicts was studied at the VA Hospital, Houston, Texas. The nephrotic syndrome was the presenting feature in all six patients and two progressed to terminal renal failure in less than a year. The renal damage appears to be secondary to immune-complex deposition with interstitial swelling, mononuclear infiltration and tubular dilatation signaling rapid deterioration of renal function and a grave prognosis; their absence indicates a prolonged, indolent course.

Treatment of kidney disease

A new test developed at the VA Hospital, Dallas, Texas, provides a sensitive and reliable noninvasive means of differentiating infection of the upper urinary tract from that of the lower tract. It consists of detecting the presence of antibody-coated bacteria in the urinary sediment, their presence correlating closely with upper urinary tract infection. This technique is applicable to the hospital diagnostic microbiology laboratory and results can be available early in the patient's management when such information is most helpful.

The clinical efficacy, tolerance, and pharmacokinetics of the new amino-glycoside antibiotic, sisomicin, were studied in elderly male patients suffering from complicated urinary tract infections at the VA Hospital, Madison, Wisconsin. Sisomicin was effective against gram-negative organisms and was well tolerated but did not offer major advantages in comparison to gentamicin.

Investigators at the VA Hospital, Nashville, Tennessee, reported a new method for achieving a desired mean serum penicillin G concen-

tration in patients with renal failure. The method, based on the linear relations between the total plasma clearance of penicillin G and of endogenous creatinine, allows minimal risk of both undertreatment and drug toxicity. Investigators at the VA Hospital, Bronx, New York, also recommended that the parenteral dose of the antibiotic clindamycin phosphate be reduced by at least one-half in patients with chronic renal failure.

Because existing symptomatic therapy for clinical hypercalcemia is unsatisfactory, investigators at the VA Hospital, Washington, D.C. examined the acute and chronic effects of the diuretic agent, furosemide, on hypercalcemia produced in animals by dihydrotachysterol plus calcium chloride. Furosemide effectively lowered elevated serum calcium concentration by increasing glomerular filtration and depressing tubular reabsorption of calcium when depletion of extracellular fluid volume or dehydration is prevented during the course of the diuresis.

Treatment of gram-negative urinary tract infections in patients with urological abnormalities—a particularly common and severe problem at VA clinical facilities—interests VA investigators. At the VA Hospital, Houston, Texas, blocking urease production by means of acetohydroxamic acid was shown to decrease the invasiveness of Proteus infections and to enhance the antibacterial effect of methenamine.

Dialysis, transplantation, and treatment of uremia

At the VA Hospital in Richmond, Virginia, the urinary excretion of sodium and water was investigated in patients with chronic end-stage renal disease in an attempt to dissociate and examine separately the effects of solute load (urea) and extracellular fluid volume expansion.

The overall excretion by sodium and water by any one patient is directly influenced by several factors including solute load, the degree of extracellular fluid volume and the glomerular filtration rate. Maximal excretion of sodium and water by the patient with chronic renal insufficiency can be obtained only at the expense of both marked azotemia and extracellular fluid volume expansion. Furthermore, a major reduction in extracellular fluid volume in the patient with chronic renal failure will almost certainly lead to a fall in blood pressure and glomerular filtration rate with further reduction in sodium excretion.

At the VA Hospital, Denver Colorado, post mortem tissue analysis of 27 patients maintained on hemodialysis for 2 to 75 months revealed significant potassium depletion in 58 percent of the patients, primarily in skeletal muscle, myocardium and brain potassium depletion was observed with all dialysate potassium concentrations but was greatest in patients dialyzed against potassium-free baths. Maintenance of normal intracellular potassium stores may require stricter metabolic control in the inter-dialytic period as well as elimination of potassium-free dialysates. The same investigators concluded that changes in muscle magnesium reflect changes in total body potassium and are not a valid indicator of total body magnesium in patients with chronic renal failure.

Electroencephalographic changes and various central nervous system abnormalities occur in patients with uremia. Investigators at the Wadsworth VA Hospital, Los Angeles, California found a significant

increase of brain calcium content in acutely uremic animals. This phenomenon was prevented by parathyroidectomy but occurred after the administration of parathydroid extract both to normal and uremic animals previously subjected to thyroparathyroidectomy. The electroencephalographic changes found in animals with acute renal failure require the presence of excess parathyroid hormone in blood, and may be related to the observed changes in the brain content of calcium.

The question of why toxic symptoms appear with altered nitrogen metabolism in uremia remains unanswered. Investigators at the Wadsworth VA Hospital, Los Angeles, California showed changes in amine oxidase activity in the blood of uremic patients and in various tissues of chronically uremic animals, suggesting that the catabolism of amines in uremia may be altered with unknown metabolic consequences.

The metabolic processes by which urea is synthesized in chronic uremia have received little attention. Researchers at the Wadsworth VA Hospital, Los Angeles, California have studied the urea cycle in uremia by measuring the plasma and tissue levels of the amino acids arising from or directly related to the cycle in patients with renal failure and in experimental uremic animals. Similar concentrations of aspartic acid and arginine occurred in control and uremic subjects while both ornithine and citrulline were elevated in uremic patients.

The anemia of chronic renal failure is important because it reduces the supply of oxygen to the tissues. To compensate, patients reduce the affinity of hemoglobin for oxygen, a process mediated by the red blood cell enzyme 2,3-DPG. At the VA Hospital, Indianapolis, Indiana, the *in vivo* P_{50} decreased significantly during hemodialysis, a fall entirely attributable to the rise in red blood cell pH by the Bohr effect. The decrease of *in vivo* P_{50} during hemodialysis may transiently impair tissue oxygen delivery in uremics and marked increase of the pH should be minimized.

Occasionally, patients with mild to moderate chronic renal failure have elevated serum potassium concentration in disproportion to the level of impairment of glomerular filtration rate. They usually have hyporeninemia, hypoaldosteronism and hyperchloremic acidosis. The role of mineralocorticoid deficiency in this newly recognized syndrome in uremic patients was investigated at the VA Hospital, Miami, Florida. The syndrome of hyperchloremic acidosis with hyperkalemia and mild renal insufficiently was usually associated with hypoaldosteronism and the hyperkalemia was rapidly corrected by mineralocorticoid treatment. The mild hydrogen ion secretory defect in some patients may be due to intrinsic tubular damage since mineralocorticoid therapy did not correct it. Patients with normal renal function and mineralocorticoid deficiency in Addison's disease or bilateral adrenalectomy exhibit only moderately impaired acid excretion and a normal capacity to excrete hydrogen ion.

Much research in nephrology concerns dialysis and transplantation with the VA developing these therapeutic modalities for end-stage renal disease patients. Investigators at the VA Hospital, Columbia, Missouri, continued work on the kinetics of coil dialyzers demonstrating that ultrafiltration rate markedly influences the dialysance of larger molecular weight solutes in coil dialysis. The same investigators studied the extent and complexity of blood-membrane interactions

during clinical dialysis. Many blood components (leukocytes, platelets, fibrin-like strands and many free-cell organelles) were deposited in the coil membranes and the deposition increased directly with the blood perfusion time in spite of using heparin with the intermittent intravenous technique.

It is difficult to determine the optimal dietary intake of vitamins in uremia because metabolism is altered and because vitamin losses during dialysis are not well-defined. Investigators at the VA Hospital, Wadsworth, Los Angeles, California, calculated the vitamin content of diets prescribed for chronically uremic patients and subjects undergoing dialysis. For thiamine, niacin, panthotenic acid and biotin, a supplement equivalent to the recommended daily allowance for normal subjects is sufficient. For folic acid vitamin B_6 and ascorbic acid dietary supplementation is needed. Excessive consumption of vitamins, particularly of the fat-soluble vitamins, in uremia may be disadvantageous.

The level of erythrocyte transketolase activity (ETKA) might correlate with the presence of uremic neuropathy but studies at the VA Hospital, Nashville, Tennessee showed that ETKA is unrelated to the peripheral neuropathy in uremia. Hemodialysis did not affect ETKA in uremic patients with proved peripheral neuropathy, nor did uremic plasma have any inhibitory effect on ETKA in erythrocytes from nonuremic patients.

There is need for sensitive, accurate, and easily performed measurements to assess the severity of uremic toxicity. Perception of short time intervals have been suggested as one such measurement. At the Wadsworth VA Hospital, Los Angeles, California, it was shown that, in patients on hemodialysis, short time interval perception is inversely related to the length of the interdialytic period, suggesting that this index may be inversely related to the severity of uremia. The instrument employed appears to provide an accurate, sensitive and easily administered technique for monitoring uremic toxicity. Investigators at the VA Hospital, Denver, Colorado demonstrated that the renin-angiotensin system is markedly activated during hyperacute hererograft rejection in a renal xenograft animal model.

At the VA Hospital, San Francisco, California, studies aimed at improving the perfusion systems employed in kidney preservation found that cryoprecipitated plasma can be replaced by colloids and that phosphate buffers can replace bicarbonate buffers. Cryoprecipitation, millipore filtration, the need for typed plasma, and the risk of virus transmission can be eliminated, as well as the need of adding CO_2 to the gassing mixture. Employing an adequate oxygenator, only ambient air is required for gassing.

Kidney function in health and disease

Continuing studies on renal hemodynamics, investigators at the VA Hospital, San Francisco, California, examined the influence on the glomerular arteriolar resistance resulting from alterations in effective blood viscosity and explained the tendency for the fraction of the plasma actually filtered at the glomeruli to vary directly with hematocrit in anemic and polycytemic states in man.

The same investigators studied the adaptive increase in glomerular ultrafiltration rate which occurs in the remaining nephrons when the

renal mass is reduced. They employed a unique strain of Wistar rats with glomeruli located on the kidney surface allowing special microphysiological techniques. The adaptive increase in the glomerular filtration rate of a single glomerulus results primarily from increases in the glomerular plasma flow and transcapillary hydraulic pressure difference.

Investigators at the VA Hospital, Oklahoma City, Oklahoma, studied the effects of histamine on the renal circulation. Injection of histamine into the renal artery of an animal lowers the renal vascular resistance and secondarily increases lymph and urine formation with no direct effect on renal vascular permeability.

At the VA Hospital, Houston, Texas, studies elucidated the factors that regulate bicarbonate reabsorption by the kidneys and control the acid-base status of the body. Parathyroid hormone acted directly on the renal tubules and decreased the reabsorption of bicarbonate. The reabsorption of urate by the renal tubules is influenced by the state of hydration and the extracellular fluid volume. Although significant differences in urate metabolism may exist between an animal and man, a similar mechanism may explain the hyperuricemia observed in man following chronic usage of diuretics.

Renal function after relief of ureteral obstruction in the experimental animal depends on whether one or both ureters have been obstructed. Investigators at the VA Hospital, Durham, North Carolina, used animals with unilateral ureteral obstruction to show that the absence of postobstructive diuresis results from marked reduction in renal hemodynamics. The filtration distribution becomes severely heterogenous with many non-filtering nephrons and a reduced delivery of filtrate to the distal parts of the nephron.

Studies done at the VA Hospital, Iowa City, Iowa, using an isolated animal kidney prepartion found that renin depletion impairs the capacity of the kidney to autoregulate blood flow and glomerular filtration rate.

The diuretic agent furosemide at large doses may alter the clinical course of acute renal failure and this phenomenon was studied at the VA Hospital, Miami, Fla. Furosemide was injected into the renal artery of six patients 2 to 9 days after the onset of acute renal failure but failed to improve renal function. Short-term administration of furosemide in large doses did not improve renal hemodynamics or alter the clinical course of patients with established acute renal failure.

Relatively little is known of the forces governing glomerular filtration in glomerulonephritis. It was demonstrated at the VA Hospital, San Francisco, California that, despite extensive glomerular injury, the glomerular filtration of an animal with nephrotoxic serum nephritis remained normal. Increased transcapillary hydraulic pressure difference compensated for the decreased glomerular capillary filtration coefficient.

Hypothyrodism in man is associated with decreased renal hemodynamics and sometimes with decreased ability to excrete water and hyponatremia. The possibility of altering sodium excertion was investigated at the VA Hospital, Miami, Florida, in patients with hypothyroidism. Several myxedematous patients were unable to achieve sodium balance or did so very slowly when challenged with a low sodium intake.

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When myxedematous patients were salt loaded their urinary excretion of sodium matched that of control subjects despite reduced renal hemodynamics. However, their capacity to conserve sodium in response to stimuli for rapid sodium conservation was diminished. Tubular reabsorption of sodium seems decreased in myxedema indicating that thyroid hormone influences normal sodium reabsorption.

Neurology and neurobiology

Multiple sclerosis

The incidence of multiple sclerosis varies from one country to another, providing clues to the cause of this crippling disease. Thus, people moving from an area of high to one of low incidence and vice versa may show when and where the disease is acquired. An investigator at the VA Hospital, Washington, D.C., reported a preliminary study of the prevalence of multiple sclerosis in a population with a normally low rate which moved to a region of high prevalence, namely Vietnamese moving to Paris. When the prevalence of multiple sclerosis was compared with that of a disease more uniformly prevalent amyotrophic lateral sclerosis (ALS), Vietnamese in Paris had comparatively less multiple sclerosis than Frenchmen generally.

The prevalence of multiple sclerosis in a small area of Romania has been investigated by a group at the VA Hospital, Minneapolis, Minn., with the finding that there are striking variations from one district to another. These variations do not correlate with several variables which have been suggested as being important in the disease; notably, climate, altitude, urban-rural differences and the level of lead in the blood. Another study from the same institution did show a correlation between prevalance and the intake of animal fat. A low fat diet might impair delayed hypersensitivity mechanisms which may underlie multiple sclerosis.

Research is also being conducted on the chemistry of the nerve myelin sheath and on neurochemical changes seen both in natural sclerotic plaques and in the animal model of multiple sclerosis, experimental allergic encephalomyelitis (E.A.E.). At Palo Alto, Calif., a VA study of regional differences in myelin composition and stability reported that differences in stability may be related to the content of the proteolipid in the myelin and may be a factor in determining the location of the lesion in the nervous system. Investigators from the same institution also report increases in proteolytic enzyme activity in demyelinating plaque in E.A.E. These increases and reported increases in protein synthesis may be associated with the presence of invading mononuclear cells.

Also reported from Palo Alto is a VA report of the role of antimyelin antibodies in the myelin breakdown seen in E.A.E. A complete dissociation occurs between the development of experimental allergic encephalomyelitis, the presence of anti-basic protein antibody and the occurrence of myelination inhibition factor, suggesting that myelination inhibition factor is not involved in the pathogenesis of experimental allergic encephalomyelitis. It also argues against a role for anti-basic protein antibody as an antimyelin factor *in vitro*. A VA study from Boston suggests that humoral antibodies may be re-

sponsible for some of the early changes in E.A.E. seen by electron microscopy, especially the early increase in vascular permeability prior to the arrival of immune cells.

Virus infections

From the virus laboratory at the VA Hospital, San Francisco, Calif., it was reported that herpes simplex Type II virus can be recovered from sacral sensory ganglia of persons with no history of symptomatic disease. Recurrent herpes genitalis thus may be caused by periodic migration of the virus down the sensory nerves to the skin; a suggestion which may be significant in view of the postulated relationship between genital carcinoma and recurrent herpes genitalis.

San Francisco investigators have also reported on subacute sclerosing panencephalitis (S.S.P.E.), a rare disease, causing intellectual deterioration, crippling and death in children and adolescents. It exemplifies a significant new concept in human medicine—that of the slow virus infection. An *in vivo* demonstration in the experimental animal of a change in the measles virus from a fully infective particle to a defective one infectious only within cells is a new finding. This significant change is apparently caused by the host antibody response, to be permanent, and may resemble early events in human S.S.P.E.

It may also parallel other slow virus or latent measles infections of the nervous system, conditions increasingly suspected of underlying many neurological conditions currently regarded as degenerative. Viral causes of congenital abnormalities of the nervous system may even account for 25–40 percent of all congenital abnormalities and represent, through mental retardation, an immense waste of human and economic potential.

Recovery from stroke

Damage to the neural tissue, whether due to physical trauma, infection or interference of its blood supply (stroke) initiates various reparative processes. Some of these processes improve the function of the nervous system; others, such as brain edema, appear to be deleterious.

In a series of experiments, investigators at the VA Hospital, Boston, Mass., showed that the functional recovery following damage to a region of the brain depends on the rate at which the damage occurred. In monkeys, the behavioral effects of a single lesion in the frontal lobe were more severe and persistent than the effects of a series of smaller lesions which actually damaged more tissue in the same area. The intact tissue surrounding the lesion seemed to play a critical role in recovery, suggesting that it is not true that specific neurological functions are rigidly performed by one specific area of the brain.

In a related development, VA investigators at the VA Hospital, Bronx, N.Y., found that regrowth and sprouting of noradrenergic nerve terminals occurs in the region surrounding a lesion in the cerebral cortex. Only 3 hours after the damage was induced in animals, signs of this increase of noradrenergic terminal activity could be detected. This research dealt with the development of seizure activity but it also contributed to understanding how functional recovery occurs.

Another group of investigators at the VA Hospital, Palo Alto, Calif., studied the growth of nerve cells when removed from the cortex of newborn animals and grown in tissue culture. Neuronal and architectural maturation in several weeks produced specific patterns of cellular organization unique to cultures of neocortex and served to distingiush these cultures from those of neutral tissue derived from different neuroanatomical regions. These observations suggest that at least some aspects of the structural growth patterns of cells in the central nervous system may be rigidly determined. Other VA research at Denver, Colorado, disclosed that a particular type of glial cell hypertrophies during the chemical injuries to the brain associated with hepatic coma. These cells may be critically important in metabolizing the excess blood ammonia levels occurring during hepatic coma.

Sensory and perceptual disorders

In the area of sensory and perceptual disorders, significant new developments have emerged from VA laboratories in the fields of vision, audition and olfaction.

Investigators at the VA Hospital, Sepulveda, Calif., studied the degeneration of photoreceptors and the neural connections of these visual cells in a recently discovered strain of mice which develop spontaneous and profound retinal degeneration in the first few days of life. Comparison of the biochemical status of these peculiar retinae with that of normal retina suggests that the inherited abnormality involves certain classes of retinal nerve cells more than others. The relationship of this acquired blindness in the mouse and human disease is not clear but its study may define critical biochemical changes in retinal metabolism which occur in human disorder.

At the VA Hospital, Martinez, Calif., investigators reported that, even in human subjects with normal hearing, a major asymmetry exists in the perception of pitch when the two ears receive simultaneous tones of different frequency. Further analysis has indicated that the spectral and intensity information of an auditory stimulus are dissociated and processed by separate channels in the nervous system. At a later stage in the neural processing, the two types of information are recombined. By developing computer-controlled audiological testing procedures, both the dissociation and the subsequent recombination of pitch and intensity information are being investigated in patients with hearing disorders due to cochlear and central nervous system damage.

The receptor cells of the olfactory organ—unlke those of the other special senses—are directly exposed to the atmosphere and are thus subject to infection (chronic rhinitis) as well as to damage by air-borne toxic material. Despite this exposure, most individuals retain their sense of smell throughout life. Other neural tissue has a limited ability to regenerate but investigators at the VA Hospital, Philadelphia, Pa., showed that olfactory receptors retain a significant capacity to regenerate. Study of this model may assist in understanding the regeneration capacity of other neural cell types.

Nuclear medicine and radiation

Instrumentation

The impact of fundamental research upon clinical medicine was recognized during the past year when Dr. William H. Oldendorf,

Medical Investigator at the VA Wadsworth Hospital Center, Los Angeles, Calif., was awarded the first *Ziedses Des Plantes Medal*, named for the Dutch pioneer radiologist, by the Physical Medicine Society of Würzburg, Germany. Dr. Oldendorf's original work in the field of neuroradiology, "Isolated Spot Detection of Radiodensity Discontinuities," was published in January 1961 in the IRE Transactions on Biomedical Electronics. It provided the basis for the development of computerized axial tomography, a technique which, when perfected by English medical investigators, revolutionized instrumentation in X-ray diagnosis. A whole new category of instruments called the CATS (computerized axial tomographic scanners) has arisen from the fundamental investigation. CATS utilizes an X-ray source and a computer system to produce cross-sectional (tomographic) X-ray images of the brain, allowing early and accurate diagnosis of central nervous system abnormalities. The new technique has now been extended to systems capable of imaging the entire body.

This year, VA investigators at West Roxbury, Mass., developed a small cadmium telluride semiconductor probe and evaluated its use in the detection of acute infectious tooth abscesses in animals following the administration of an isotope radiopharmaceutical, Technetium-99m polyphosphate. The isotope uptake detectably increased in abscessed teeth within one to two weeks after infection; intra-oral X-rays required four weeks for positive detection. The cadmium telluride probe distinguished contiguous normal and infected root tips less than 1 cm apart whereas the standard sodium iodide detectors were unable to distinguish normal root tips of an uninfected tooth between those of two adjacent infected teeth.

The idea that computers can better define lesions which are demonstrated on Nuclear Medicine scanning equipment led VA investigators at Milwaukee, Wisc., to develop and prove a method using a mini-computer to enhance lesions demonstrated in patients by scintillation camera images. The technique makes enhancement by fast fourier transform techniques available to all Nuclear Medicine laboratories that have mini-computers. A different approach by VA investigators at Gainesville, Fla., developed a computer program that eliminates gamma ray scattering within the patient and the penetration of the collimator septa. Correction for these and for nonuniformity of the instruments' crystal response significantly improved Technetium-99m brain scans in those regions with the most activity. Non-radioactive lesions of the liver, not defined by raw images, were made manifest by computer-processing. The computer program provides greater validity of radionuclide distribution and assists in improving diagnostic accuracy.

An image intensifier camera was developed at the VA Hospital, Denver, Colo. This special high-sensitivity gamma-ray stationary imaging device is ideally suited for performing dynamic studies of the heart and great vessels. This is the first medical application of a unique light-sensing device linked to a digital computer for the diagnostic use of gamma rays.

Another approach to the use of computers in Nuclear Medicine was provided by the VA group at St. Louis, Mo. Data obtained from patients by uniform, standardized techniques using radioisotopes are entered directly into computers and transmitted by telephone to a

central site at the John Cochran Hospital in St. Louis where the results are interpreted. In this manner the VA hospitals at Jefferson Barracks, Mo., Marion, Ill., and Poplar Bluff, Mo., conduct and receive the results of static and dynamic studies without having a Nuclear Medicine physician in residence. The technologist's use of the equipment at each hospital is simple and the telephone transmission of images is accurate enough to provide efficient diagnostic services.

Radiopharmacy

New procedures in nuclear medicine often require the development and production of radiopharmaceuticals which concentrate in specific areas of the body, allowing diagnosis of specific abnormalities. The VA group at Los Angeles, Calif., reported the development of a technetium-penacillamine-Acetozolamide complex for renal scanning and has used the new agent to diagnose various kidney diseases. The substance localizes in the renal cortex and is cleared very slowly from the circulation producing excellent renal images. Technetium-99m-penacillamine, a pharmaceutical of great promise in visualization of the gall bladder, was investigated by the same group which also developed I-131- and Technetium-99m labeled metronidazoles as agents to reveal amebic hepatic abscesses. Studies throughout the world have demonstrated the latter's efficacy in the diagnosis and localization of such abscesses. Indium 113m sulfide macroaggregate, an excellent lung scanning agent, was found to be easily prepared and useful where Technetium-99 compounds are not available.

VA investigators at Hines, Ill., described an improved generator devised as a prototype to provide continuous production of 81m Krypton for clinical use. The Krypton may be delivered as a liquid or a gas, has a half-life of 13 seconds and emits gamma rays which are ideal for imaging. Krypton 81m allows the selective visualization of blood vessels, determination of the size, configuration and location of infarcts as well as localization of vascular insufficiency and pathologic sites of absent, increased or decreased circulatory exchange. When infused at a constant rate into the artery leading to an organ or an anatomic region, the gas reaches equilibrium. In this steady state radioactivity remains constant within the blood vessels but the gas diffuses into the extra-capillary space and then changes more slowly than the gas in the vessels. Thus, still pictures can reflect the adequacy of capillary exchange.

At the VA Hospital, Sepulveda, Calif., methods of producing aminoacids labeled with 13 nitrogen have been developed. Nitrogen 13 has a half-life of 10 minutes, but it is used as a label to map the body distribution of many compounds. Most compounds have been labeled by slow and uncertain methods. The investigators developed an enzymatic synthesis which is rapid, produces no intermediates and yields a specific end-product. Satisfactory 13 nitrogen-L-alanine has been synthesized by binding the two required enzymes on a solid support so that the end-product contains none of the enzymes. Usually antibodies are conjugated with various non-radioactive compounds in order to locate antigen-antibody reactions at the cellular and intracellular level.

At the VA Center, Los Angeles, Calif., radionuclides such as Indium 111 were bound to antibody without destroying its ability to participate in immune reactions. Transferrin, d-penacillamine and desferoxamine were conjugated to antibodies by a coupling compound without losing their reactivity.

At the VA Hospital, San Diego, Calif., a new non-stannous renal scanning agent, Technetium-99m thiomalic acid, was developed. It compares favorably with available kidney scanning agents and avoids tin's interference with subsequent studies in which Technetium-99m pertechnetate is used as a diagnostic agent.

At Ann Arbor, Michigan, investigators evaluated twenty-four selected testosterone analogs using prostatic tissue in order to discover a compound that would visualize and possibly treat prostatic carcinoma and its metastases. The results suggest that such a compound is feasible.

Tumor diagnosis and treatment

In order to study bone imaging for the early detection of skeletal metastases, research into the kinetics of polyphosphate and diphosphonate labeled with Technetium-99m has been pursued at the VA Center, Los Angeles, Calif. VA groups at Los Angeles and St. Louis, Mo., have demonstrated that bone images with Technetium polyphosphate are sensitive indicators of bone lesions and are superior to X-ray examination or previously utilized radio-nuclides for the early detection of bone metastases. With low toxicity, ready availability, economy, shortened procedure time, and a low radiation dose, new bone seeking compounds are now the agents of choice for searching for bone metastases.

Studies have also demonstrated the utility of bone-scanning in the assessment of other disease entities. At the VA Hospital, San Diego, Calif., the use of the bone-scan as an early sign of degenerative arthritis was compared to physical evaluation, plane X-rays, and arthrograms in 60 patients undergoing evaluation for surgery. Surgical arthroscopic examinations were obtained in 20 joints. In the less involved joints, the bone-scan was most sensitive to pathology, the arthrogram second and the plane X-rays third. Physical examination was least sensitive. At Los Angeles, VA investigators found pyrophosphate kinetics and imaging to be very sensitive for the early detection of skeletal lesions in pseudo-hypoparathyroidism and the most sensitive diagnostic imaging procedure revealing bone lesions in primary hypoparathyroidism.

At the VA Hospital, Tuscon, Ariz., Gallium-67, a radio-pharmaceutical which concentrates in soft tissue tumors, was compared with 111-Indium-labeled bleomycin, an anti-tumor antibiotic. Ninety percent of involved sites were correctly identified with Indium-labeled bleomycin but with no greater specificity than Gallium-67. More tumor types have been visualized with Indium-labeled bleomycin, especially gynecological and gastrointestinal tumors and it does not accumulate in the intestine.

VA investigators at San Diego, Calif., evaluated a radionuclide staging protocol for bronchogenic carcinoma. The radionuclide search for metastases included liver, brain and bone scans using Technetium-99m labeled radiopharmaceuticals and Gallium-67 Citrate imaging.

Among the first 30 patients studied preoperatively ten went to surgery; 100 percent of the tumors were resectable at thoracotomy. This contrasted with previous experience; only 60 percent of unsearched patients had resectable lesions. Gallium-67 imaging of the chest confirmed that nearly 100 percent of bronchogenic carcinomas take up the radionuclide.

In a search for new radiopharmaceutical agents that are more useful in the characterization of tumors, another group of VA investigators at San Diego evaluated and developed radioiodinated tetracycline as a tumor scanning agent. In animals bearing an implanted hepatoma I-131 tetracycline compared favorably with Gallium-67 as a tumor-scanning agent and more frequently demonstrated tumors with some degree of necrosis.

Investigators at the VA Hospital, Hampton, Va., evaluated treatment with 32-P of severe bone pain from diffuse metastic tumors, especially prostatic carcinomas. Radioactive phosphorus alone did not work; however, parathormone in conjunction with radioactive phosphorus was very effective in relieving bone pain.

Central nervous system

The VA group at Brooklyn, N.Y., has described the selectivity of phlorizin as an inhibitor of glucose transport. The presence of a phlorizin-reactive cell type in the ventro-medial hypothalamus suggests that special gluco-receptor cells in this area are involved in the regulation of food intake. VA investigators at San Diego, Calif., injected hyperbaric solutions of amphotericin and dextrose mixed with I-131 albumin into the lumbar space of monkeys. When placed in the Trendelenburg position (feet elevated), the animals had higher cisternal concentrations than monkeys given non-hyperbaric solutions and kept supine. This technique may prove useful in the treatment of fungal meningitis.

At the VA Hospitals, Palo Alto, Calif., and Minneapolis, Minn., the use of radionuclides and the gamma camera in the visualization of blood flow was evaluated in patients with carotid-cavernous sinus fistulae. The technique is simpler, less traumatic and less hazardous than older methods.

At St. Louis, Mo., VA investigators demonstrated decreasing peritumor concentration in brain scans performed with Technetium-99m pertechnetate following the administration of a cortico steroid for the treatment of cerebral edema. The apparent decrease in tumor size was due to a diminution in edema around the tumor.

Cardiovascular studies

Various aspects of cardiac function have been examined using a gamma camera and computer processing following the administration of intravenous radionuclides. At the VA Hospital, Seattle, Wash., animal studies confirmed that the visualization of myocardial blood flow at rest and during stress provides new diagnostic information. In approximately 200 patients, the radionuclide method proved more sensitive than clinical history, EKG or coronary arteriography in detecting areas of scarred myocardium. The technique determined the effect of coronary arterial constriction on blood flow to the working heart, and identified arteries which need surgical therapy. In addi-

tion, VA groups at Miami, Fla., and Hines, Ill., have evaluated the concentration of a radiopharmaceutical, Technetium-99m-labeled phosphate, in acute myocardial infarctions. This procedure shows promise in the diagnosis of acute myocardial infarction.

At San Diego, a non-traumatic and non-invasive radionuclide technique was developed for determining cardiac function. It appears particularly useful for the serial evaluation of acutely ill patients and for followup of non-hospitalized patients.

Investigators at the VA Hospital, Denver, Colo., have utilized non-invasive radionuclide techniques and computer processing in order to determine mitral and aortic valvular insufficiency. There was close agreement with conventional contrast angiographic studies with the advantage that the radionuclide procedure does not require cardiac catheterization.

Miscellaneous

At the VA Hospitals in St. Louis, Mo., and Pittsburgh, Pa., bone marrow scanning was used to evaluate most of the blood forming tissue of the body. Patients with various blood disorders could be partially classified according to the pattern of the bone marrow scan. Such scanning helps locate tumors or malignant diseases involving the bone marrow, liver or spleen as well as diseases such as sickle-cell anemia associated with increased bone marrow activity and the marrow expansion into bones that are not normally blood-forming organs. The techniques also determine bone marrow death and serial studies of patients with chronic myelocytic leukemia suggest that the bone marrow scan may be of prognostic significance. At St. Louis, studies on transplanted kidneys demonstrated that Technetium-99m sulfur colloid uptake by the transplanted kidney helps to differentiate acute tubular necrosis from transplant rejection. The diagnosis can be established prior to other diagnostic changes and allow prompt initiation of appropriate therapy.

Nursing research

Projects by nurse researchers provide evidence of their commitment to improve patient care through clinical nursing research. At Salt Lake City, Utah, a VA-Brigham Young University study indicated surprisingly low correlations between patient-care scores and performance scores. Education was related positively with patient care and nursing performance measures. A VA research study partly sustained the hypothesis that patients on medical-surgical units report less omissions in nursing care when the pattern of care is primary nursing than when it is team nursing and that satisfaction with care was higher in the primary nursing group than in the team nursing group of patients.

Two studies dealt with the evaluation of structured means of nursing assessment or data-gathering and provided information in a major area of concern: at the VA Hospital Center (Wadsworth), Los Angeles, Calif., investigators studied nursing assessment and care plan statements, and at the VA Hospital, Long Beach, Calif., others developed a patient-completed admission questionnaire and compared it with the nursing interview.

For many years it has been recognized that good relationships between physicians and nurses improve patient care and that the separatism between medical and nursing education may produce physicians who are insensitive to the knowledge and skills of nurses and other health professionals. A study at the VA Hospital, Madison, Wis., evaluated one method of introducing nursing procedures to medical students. Most medical students felt that the experience was valuable and that the trials should be continued.

Half of all VA Hospitals have a Nursing Research Committee, teach a course in research methodology for nursing staff, use a nursing research consultant on a regular basis, and/or participate in research studies directed by large outside organizations such as Western Interstate Commission on Higher Education (WICHE), Southern Regional Board of Education (SREB) or Division of Nursing (NIH–HEW). During the past year, VA nurse researchers participated and presented papers at 5 Nursing Research Conferences: at VA Hospitals in Shereveport, La.; San Antonio, Texas; Prescott, Ariz.; Murfreesboro, Tenn.; and at Central Office Nursing Service, Washington, D.C. In addition, doctoral nurse researchers and the Chief Nurses at their sites met at Palo Alto, Calif., to discuss research in the patient setting. These conferences were attended by large numbers of VA nurses and by university faculty members involved in joint VA-University investigations. Doctoral nurse researchers are located in fifteen VA settings.

Oncology

The VA has pioneered in clinical studies of therapy for neoplasms common in veterans and VA hospitals provide the largest, most uniform group of patients with neoplasia available for trials of new therapeutic agents or approaches to cancer. In order to carry out such studies, the Veterans Hospital Cooperative Research Groups with representatives from VA hospitals throughout the country develop uniform protocols for the therapy of various types of neoplasms.

Because large numbers of patients can be treated according to such protocols the VA Cooperative Groups can answer clinical questions promptly and efficiently. Such VA studies have provided definitive answers to important clinical questions regarding the optimal management of such common diseases as carcinoma of the prostate, of the lungs, and of the colon and rectum.

The study of rectal cancer, for example, has demonstrated an increased five-year survival rate, to 47 percent, for patients undergoing surgery and treated with pre-operative x-ray therapy when compared to only 34 percent of those treated with surgery alone. The preoperative radiation therapy was able to lower the percentage of patients with carcinoma, metastatic to lymph nodes, from 45 percent to 27 percent.

Another VA Cooperative Study concerns the treatment of non-resectable cancer of the lung using only chemotherapy of various types when compared to combination treatment with radiation therapy and chemotherapy. The results to date indicate that no combination of drugs or combined therapy is superior to treatment with cyclophosphamide alone.

The VA Cooperative Urologic Research Group correlated the pretreatment serum corticosteroid values with the survival of patients with prostatic cancer. The higher the initial value of serum non-protein bound cortisol and 17-hydroxy corticosteroid, the greater the probability of death during the first year of treatment, regardless of the treatment or stage of the disease.

The increasing emphasis on basic research related to cancer has resulted in the establishment of a Merit Review Board in Oncology. The multidisciplinary nature of its membership has strengthened the ability of the Board to provide expert review of proposals and to suggest improvements in experimental design.

VA Hospital, Salt Lake City, Utah, has reported new findings on the role of macrophages in resistance against cancer. Macrophages which are present in all tissues have generally been considered to be scavenger cells that remove foreign material and dead cells in order to maintain a constant internal environment. The VA investigators established an important role for macrophages in the recognition and destruction of tumor cells as well. Macrophages which have been activated by immune stimulants such as bacilli Calmette Guerin (BCG) have the ability to recognize specifically and to destroy tumor cells while leaving normal cells unharmed. Macrophages destroy tumor cells by the transfer of lysozymes, which are subcellular structures containing toxic chemicals, to tumor cells. These lysozymes of macrophage origin then cause the destruction of the tumor cells. Although these studies were conducted with experimental animal neoplasms, improved knowledge of the natural defenses against tumor growth in animals may lead to more rational treatment for human cancer and to an understanding of the mechanism of action of immunotherapeutic agents already being used in man, such as BCG.

At Minneapolis, Minnesota, VA researchers demonstrated that patients with bladder cancer have lymphocytes capable of killing bladder cancer cells in tissue culture. The investigators also found that some patients with transitional cell carcinoma of the urinary tract have sera which contain (IgG) antibodies and induce lymphocytes obtained from normal subjects to kill transitional cell carcinoma target cells specifically. These antibodies may prove useful in the immunotherapy of bladder cancer. The same investigators found that the serum from some patients with carcinoma of the kidney contains antibodies which can act alone to kill tumor cells in tissue culture.

At the VA Hospital, Oklahoma City, Oklahoma, investigators found factors in the serum of patients with leukemia which impair the function of the lymphocytes responsible for cellular immunity against cancer. They have observed that a significant decrease in the inhibitory activity of the serum from leukemic patients occurs during remission and reappears with relapse.

At Denver, Colorado, VA investigators studied the role of immunosuppression by drugs during organ transplantation on the development of malignancies in these patients. The immunosuppressed organ homograft recipients showed an increased incidence of malignancies to 5.6 percent incidence some time after transplantation.

At Washington, D.C., the VA and the National Cancer Institute have developed a joint inter-agency unit, located at the VA Hospital.

This 30-bed unit has three functions: (1) to provide intensive workup and treatment of VA patients in consultation with the medical staff; (2) to evaluate the role of new anticancer agents in the management of neoplasms commonly occurring in VA patients; and (3) the treatment of patients with lung cancer, the most commonly lethal cancer in the United States. Current studies concern the development of chemotherapy with new combinations of drugs for lung cancer and the natural history of lung cancer in man.

At Milwaukee, Wisconsin, VA investigators observed that bronchogenic carcinoma with metastases to the liver induced the formation of alpha-feto protein in the surrounding normal liver cells. Since alpha-feto protein is thought to be found only in the serum of patients with primary liver cell cancer and embryonal carcinoma, the mechanism by which the bronchogenic carcinoma cells induces the normal liver to produce alpha-feto protein may be of considerable importance.

At Sepulveda, California, a specialized unit for the care and study of cancer patients has been established and investigators have been involved in studies of cancer treatment by surgery and immunotherapy BCG, a live but attenuated bovine tuberculosis baccillus, is used as an immunotherapeutic agent against cancer. Since it is given as a living vaccine to cancer patients, many of whom have a depressed immune system, patients may occasionally develop a form of a typical tuberculosis caused by the living BCG organisms. The simultaneous administration of isoniazid, a drug effectve against tuberculosis can prevent this and VA investigators demonstrated that the drug does not interfere with the antitumor effectiveness of the BCG in animals. The same investigators found that BCG immunotherapy can be a two-edged sword causing either tumor regression or enhancement of tumor growth depending upon the method of its administration to animals with transplantable tumors. Conditions for achieving optimal immunotherapy are important information for immunotherapy in man.

Investigators at Sepulveda and UCLA, investigating immunotherapy with BCG and other immune stimulants in the management of human neoplasmas, have found that BCG increases the immune response of tumor-associated antigens in melanoma patients.

Investigators have found that many cancer patients' immune systems are defective as judged by their ability to develop immune reactions to common skin test antigens or to be sensitized to new antigens such as dinitrochlorobenzene. Patients who are immunologically unreactive to these antigens have a greater chance of developing recurrence following cancer therapy than patients whose immune systems are normal. An important finding is that this immune nonresponsiveness does not exist before cancer develops but is a result of the cancer itself. For this reason, the immunosuppression can be reversed in some patients by removal of the cancer.

VA investigators have developed new tests to study the ability of a patient's leukocytes to respond to tumor antigens. The new techniques have demonstrated the presence of tumor-associated antigens in carcinoma of the lung; an observation which may have significance for immunotherapy in lung cancer. In addition, serum antibodies in cancer patients are bound to tumor cells where they may play an important role in inhibiting tumor growth or in inhibiting the patient's lymphocytes from causing tumor destruction in the patient's body.

The VA–NCI medical oncology branch

Illustrative of VA capability in cooperative clinical studies, and unique, successful, and long-term demonstration of inter-agency collaboration is the VA–HEW program on evaluation of cancer therapies. Initiated in 1956 by an invitation from the National Cancer Institute to the VA Department of Medicine and Surgery, this program gave rise in 1957 to three separate multi-VA hospital collaborative study groups involving a total of 53 separate clinical services in VA hospitals focusing on cancers of the lung in several aspects, stomach, colon-rectum, and a series of hematogenous tumors as well as multiple myeloma and malignant melanomas. Two of these programs have continued through the years. Others have been initiated or phased out. All have undergone periodic pruning for efficiency along with various evolutionary changes, reorganizations and reorientations in keeping with modernization of cancer therapies, promising leads in new directions, and some variations in available clinical material reflecting the frequency of various cancers in the population of VA beneficiaries.

These programs provide both training grounds for medical students, residents and staff in VA hospitals as they come in contact with these efforts at improvement of cancer therapy, and a means for providing increased diagnostic and therapeutic attention to a far larger number of VA cancer patients than those actually included in the treatment programs. The latter is true since most VA patients entering participating VA hospitals suffering malignancy, are carefully studied to determine whether they might in fact be included as study subjects. From this standpoint, the studies are a distinct enhancement of care for a large number of VA patients suffering from cancer.

As VA patients, subjects are fully supported by the VA Department of Medicine and Surgery in hospitalization, diagnostic studies and all aspects of their treatment and followup care. Therefore, costs to NCI for the VA cooperative clinical trials are kept to a minimum. Major allocations of NCI funds are for personnel and mechanisms of uniform study data collection, collation and analysis, and for meetings of investigators monitoring the program and discussing and reporting study plans and results.

At present, there are three cooperative studies under the interagency VA–NCI agreement, and a fourth, the VA Urology Cooperative Study Group, is funded through the NCI grants mechanism. All are described later in this report under the section "Multi-Hospital Research—Cooperative Studies in Cancer."

An additional collaborative program under the interagency agreement was initiated in 1968 at the VA Hospital, Washington, D.C., where joint VA–NCI staff are engaged in a series of integrated basic and clinical studies directly related to patient problems.

The program with its overall approach to clinical cancer and more basic practical problems related thereto is considered by both VA and the NCI to be an economic and professional enhancement to the objectives and programs of both agencies.

Oral biology

The oral disease and dental research program in the VA is broadly based. Apart from the dental profession, 14 other biomedical disci-

plines are engaged directly and indirectly in investigations of oral disease and related dental health problems.

Dental caries and periodontal diseases, the most endemic of mankind's disorders, continue as major targets of the VA research program in oral biology. Dental caries has been shown to be multifactorial, involving interactions between the human host, diet and microorganisms. At the VA Hospital, Miami, Fla., investigators recently discovered that caries-producing oral bacteria selectively or preferentially metabolize and attack certain salivary proteins which differ from the salivary proteins metabolized by non-caries-producing bacteria. This raises the question of whether an individual's saliva composition is an important determinant of caries production. Also a prognostic test for dental caries may be developed on such criteria. Current studies are determining whether caries attack rates can be correlated with salivary levels of the involved proteins.

The Miami researchers are also pioneering the investigation of new antibiotic substances of a highly selective nature, called bacteriocins. These substances are highly toxic for certain bacteria but are produced by closely related bacteria. The investigators are isolating and characterizing known bacteriocins and are seeking new ones made by non-caries producing organisms. This approach may also prove useful in the control of periodontal diseases.

Saliva is involved in both dental caries and periodontal disease. At the VA Hospital, Houston, Texas, a unique influence of light upon salivary secretion was reported previously. It has been shown recently that darkness significantly decreases salivary secretion in the resting parotid gland while varied light sources were equally effective in maintaining higher flow rates. The importance of these phenomena in dental caries was shown first in studies; different rates of caries production were associated with exposure of experimental animals to different kinds of light sources. A collaborative study of the influence of light sources upon dental caries, by the VA Hospital, Hines, Ill., and the Sarasota, Fla., County School Board, then showed that full spectrum light sources were associated with a lower incidence of caries in school children than were cool-white fluorescent sources.

A Normative Aging Study at the VA Outpatient Clinic, Boston, Mass., is designed to follow changes in human organ systems and functions as a result of the aging process. It includes saliva and salivary gland research. Recent data from this study showed that levels of certain components of saliva including sodium, chloride, calcium, protein, amylase and PH, decrease with age while the urea content of saliva increases with age. These changes reflect various aspects of glandular function. Thus, low sodium and chloride levels reflect less effective transport mechanisms of the glands while low calcium, protein and amylase concentrations are related to decreased protein synthesis. The increase in urea levels may reflect diminishing kidney function as a result of the aging process since salivary urea levels correlate closely with blood levels of urea.

Continuing studies of the intermediary metabolism of gingiva in health and disease at the VA Hospital, New York, N.Y., have demonstrated that mild and severe inflammatory states influence key oxidative enzymes of the gum tissue in different ways which appear related

to both degenerative and proliferative responses within the tissue. In addition, gingival tissues were separated and fractionated into separate sub-cellular components before the protein and enzyme distribution within each component was characterized. The resulting data could then be related to such tissue processes as mitosis or cell division, protein synthesis and drug detoxification.

The restoration of diseased tooth and oral structures constitutes the major and most costly aspect of dental care and the physical and chemical properties of restorative materials for such purposes are critical. At the VA Hospital, Sepulveda, Calif., the physical properties of dental restorative materials as well as the principles of design of dental and oral restorations receive intensive study. Utilizing a comprehensive variety of test procedures including photoelastic stress analysis, fluorescence, histopathology, and standard mechanical property tests, a variety of plastics, adhesive materials and metal alloys are being screened. Recent work has concerned the possible development and use of non-precious metal alloys.

At the VA Hospital, Ann Arbor, Mich., model systems are being developed to permit establishment of a tooth bank, in which teeth would be stored for future re-implantation. Optimal temperatures, media and other parameters for tooth storage are emerging from this work which now uses experimental animals. Histopathologic and radio-autographic techniques of analysis used to evaluate the re-implantations have indicated that it is feasible to establish tooth banks for humans.

Pathology

VA pathologists and laboratory scientists have investigated and reported on a wide variety of subjects concerned with the diagnoses or mechanisms of disease processes. Only a representative few studies will be described below.

By means of electron miscroscopic studies, VA pathologists at New Orleans, La. were able to relate changes in cell structure to treatment and to the clinical status of a patient with Whipple's Disease. The cause of this uncommon but serious disorder, which occurs primarily in adult males, is still uncertain and the findings of this study suggest that the primary defect may be located within subcellular structures called lysosomes which play an important role in defending cells against infectious agents.

At Bronx, N.Y., VA researchers found that high doses of Vitamin C taken with meals may destroy significant amounts of another important vitamin (B_{12}). The study emphasizes the possible hazards of the injudicious use of high doses of vitamin C as a home remedy against the common cold, particularly when taken with meals.

VA pathologists from Albuquerque, N. Mex., studying the effects of x-rays on blood cells, reported differing degrees of sensitivity to radiation depending upon the origin and functions of such cells. They detected differences by a relatively simply laboratory procedure. These studies have potentially important implications in our understanding of immune mechanisms.

A VA pathologist at Hines, Ill., studied the effects of the antitumor drug Vincristine on normal and leukemic blood cells and demonstrated that, *in vitro*, this drug can kill resting, as well as dividing cells, but that leukemic lymphocytes were 10 times more sensitive to the drug than normal lymphocytes. These studies are important in understanding how some therapeutic agents exert their antileukemic effect.

The development of atherosclerotic changes in vein grafts following sorto-coronary vein bypass surgery was reported by investigators at Wood VA Center, Milwaukee, Wisc. Their observations have important implications in evaluating the long term benefits of this increasingly common surgical procedure.

At Palo Alto, Calif., VA researchers reported for the first time that malarial parasites can invade blood elements called platelets which play an important role in blood coagulation. This observation may explain some of the complications of malaria.

VA researchers at Denver, Col., devised a convenient small animal model for the study of brain changes and coma due to ammonia intoxication. The changes occur very frequently in patients with severe liver disease due to alcoholism. The availability of the model provides a convenient means of evaluating different therapy and should lead to a better understanding of the mechanisms involved in this life-threatening condition.

A VA pathologist at San Diego, Calif., devised a rapid and sensitive method for measuring serum haptoglobin, a protein compound which binds free hemoglobin in the blood stream. Haptoglobin assays are important in studies or reactions to blood transfusions, in diagnosing certain forms of anemias and in assisting to determine the cause of jaundice.

A study of liver biopsies of drug addicts by pathologists at the VA Hospital, Houston, Texas, revealed a high incidence of tissue changes of a type usually associated with a foreign body reaction. These findings suggest that the filler substance usually present in street narcotics used intravenously are probably responsible for these tissue alterations.

Rehabilitation medicine

Rehabilitation Medicine Service (RMS) in the VA employs interdisciplinary therapeutic teams to improve the physical and social function of veterans and to facilitate their adjustment to life in the community. Research in rehabilitation medicine concerns new methods of diagnosis and treatment in this area including joint research with members of allied disciplines, such as psychologists and orthopedic surgeons.

Studies at the VA Hospital, Buffalo, N.Y., aimed at improving the gait of hemiplegic and other neurologically disabled patients. The flexion reflex which lifts the foot and leg in response to electrical stimulation of the sole was used in the gait retraining of hemiplegic patients. Electrical stimulation synchronized with the patient's attempt to walk, reinforced the weak flexor muscles of the partially paralyzed limb and assisted in the process of learning to walk.

Eventually, all the patients tested learned to walk without further assistance from this device but it permitted earlier gait training when the limb was still too weak to permit ambulation using conventional methods.

The same group evaluated three forms of conventional below-knee bracing commonly used for hemiplegic patients. Using force transducers, they demonstrated the hazard of knee instability with the 90° plantar-flexion stop brace as compared to two safer ones, the free-ankle and dorsi-flexion assist.

A multi-disciplinary study involving the Biomechancis Laboratory of Case Western Reserve University, orthopedic surgeons and the Rehabilitation Medicine Service, VA Hospital, Cleveland, Ohio, was based on previous experience recording the force and loading measurements from microcircuitry instrumentation of a nail implanted in the thigh bone to treat a broken hip. The nail telemetered the forces imposed on it by activities of daily living during the recovery period.

This technology has now been applied to prosthetic knee joints. Instrumented knee joints are being used to study the forces on this prosthesis during the critical post-operative period and as the patient resumes normal activities.

The VA Hospital, Long Beach, Calif., is developing a clinical, teaching and research program focused on the common myofascial pain syndrome. Patients with shoulder girdle and low back pain usually have palpable bands in the involved muscles and the bands contain trigger points for referred pain but their nature has been controversial. An electromyographic study showed a transient contraction of the muscle in response to a specific palpation technique. This suggests that the palpable characteristics of the band depend, at least in part, upon the manner of palpation.

An interdisciplinary study at the VA Hospital, Salem, Va., examined results of an 84-day alcoholism treatment program. The regimen is based on traditional socio-psychological treatment combined with a physical fitness program. Entry phychological testing and physical fitness testing used the average score of six functional measures and showed that depression is a cardinal characteristic of a person hospitalized for alcoholism. Patients gave test responses characteristic of immature anxious persons in poor physical condition. Following treatment, depression and blame projection decreased as physical fitness increased. This newly-validated testing technique is being used to determine which patients respond best to which kind of treatment.

Research at the VA Hospital, St. Cloud, Minn., offers an example of an interdisciplinary approach. A local grade school and the hospital's rehabilitation staff conducted a remotivation program for elderly, mentally ill patients in close cooperation with the Psychology Service and the community. More than 200 sixth-grade children from social studies classes demonstrated the value of a regular, structured remotivation program held by the school children in the hospital. Objective measures showed significant improvement in patient attitudes and independent functioning. The elderly veterans thoroughly enjoyed and were stimulated by their youthful friends who were in turn delighted and reinforced by their appreciation responses.

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The Kinesiology Research Laboratory of the VA Center, Wood, Wis., with the Orthopedic Service measured objectively the physical characteristics of gait using sophisticated kinematic and electronic equipment. There was an initial rapid gain in gait pattern during the first six months after a McKee-Farrar total hip replacement and most patients continued to improve for 24 months. This correlated closely with subjective clinical impressions. Such a study could objectively compare the results of different artificial hip procedures and variations of them. The laboratory developed a simple and effective force platform to measure postural stability and steadiness. Normal, stable subjects permitted a wide variation in the area over which weight is safely shifted while the average center of pressure remains remarkably close to a central point. This system provides an accurate, objective method of measuring the degree of postural stability so essential to safe ambulation in hemiparetic veterans and veterans with other neurological disabilities.

Respiration and pulmonary disease

Humoral mediators of lung disease

VA hospitals in Dallas, Tex., Wood, Wis., and Tucson, Ariz., report progress in the identification and measurement of chemical agents that may medicate a variety of pathologic processes in the lung. These processes include the bronchoconstriction of asthma, the rise in pulmonary vascular pressure associated with reduced oxygenation of the tissues and with pulmonary embolism and the fall in systemic arterial pressure complicating serious lung infections, pulmonary embolism and lung injury.

Cancer of the lung—by far the most common cancer in veterans—may be detectable at a relatively early stage by special blood tests. These tests depend on the radioimmunoassay of hormones, normally not detectable, but increased in patients with bronchogenic carcinoma. A report from the VA Hospital, Bronx, N.Y., discusses the measurement of ACTH, a hormone normally secreted by the pituitary gland, as a screening device for identifying patients with early lung cancer.

VA medical investigators at Dallas, Tex., reported that a new hormone, vasoactive intestinal polypeptide (VIP), is elevated in observed cases of watery-diarrhea syndrome, and several oncogenic tumors, indicating that excess VIP appears to be a cause of chronic watery-diarrhea and may be derived from any of several different tumors. They also reported elevations in plasma VIP levels in some patients with lung cancer. VIP is an intestinal hormone; however, another related peptide is produced in the lung. It is probably this peptide that is being measured by the assay. Current trials will determine whether the test is satisfactory for screening patients.

Investigators at the VA Hospital, Seattle, Wash., reported that natural human fibrinopeptides have no effect on respiration and circulation in animals.

Infectious diseases

Severe lobar pneumococcal pneumonia is often associated with presence of bacteria (pneumococci) in the blood stream and carries a relatively high mortality, especially in older patients. The possibility

of preventing a large number of these serious pneumonias by a program of vaccination has been investigated at the VA Hospital, Nashville, Tenn.

They found that 60 percent of 43 patients with bacteremic pneumonia and 55 percent of patients who died from their infections would theoretically have benefited from an immunization program designed to include all persons 50 years of age and older, and all younger patients with recognized underlying disease.

More precise identification of bacteria responsible for causing lung abscess and other acute bacterial infections of the lung should lead to more effective treatment by selecting the most appropriate drugs. This research is being carried out at the VA Hospital, Sepulveda, Calif.

A study of bacteria isolated from primary lung abscesses followed by antimicrobial therapy selected according to the type of bacteria present in the abscess, was judged successful in all cases by investigators at the VA Hospital Center, Los Angeles (Wadsworth), Calif. Another study at this same hospital, found that anaerobes ("undoubtedly the most overlooked bacterial pathogens of the lower respiratory tract") were the predominant cause of aspiration pneumonia and a major cause of empyema.

Tuberculosis of the lung remains a health problem, even in the United States where 30,000 known new cases appear annually and hundreds of thousands of persons have relatively controlled disease. VA research in this area has included studies at Long Beach, Calif. and Madison, Wis., of the metabolism of the causative organism.

Long Beach investigators found that 3-amino 1,2,4-triazole stimulates the catalase produced by Mycobacterium tuberculosis in contrast to its inhibitory effect on catalase from other sources. Another study at this same hospital, of vaccination with BCG (bacillus Calmette-Guerin) found that there was no significant difference in the tuberculosis bacilli recovered from animals' spleens or lungs, regardless of the age of the culture, the cultural conditions, or the immune status of the host. Madison VA investigators found that by exposing Mycobacterium tuberculosis to isoniazid, it inhibited cellular mycolate synthetase activity and that the activity was reactivated after a time-lapse in exposures of up to 10 hours. The inhibition became irreversible in exposures of more than 10 hours. Rifampin in twice as potent a dose was shown to limit protein in M. tuberculosis but only moderately inhibited cellular mycolate synthetase activity. Hence, the restoration phenomenon is thought not to involve protein synthesis.

An interesting discovery of infectious particles called "xenosomes" was reported from the VA Hospital, Miami, Fla. These self-replicating protozoa, smaller than bacteria but larger than viruses, may provide a better understanding of DNA replication which is important in all cell functions, and of the nature of the infectious process.

Diagnostic techniques

Research at VA Hospitals in Indianapolis, Ind. and Denver, Colo., has confirmed that it is possible to obtain lung tissue for histologic or pathologic examination through the flexible bronchoscope. The method is simple and relatively free from serious hazard.

Other techniques of diagnostic value have been under investigation in a number of VA hospitals. VA investigators at Oteen, N.C.,

reported on the dangers of needle biopsy of the lung, naming several "cutting type" needles which they condemned because of the number of severe hemorrhages reported after their use.

At the VA Hospital, Gainesville, Fla., investigators reported a simple, practical method of estimating the function of human lungs after surgery. Experience in 13 cases shows that a number of vital post-pneumonectomy functions can be predicted.

In Denver, Colo., VA investigators compared radiocardiography with dye dilution as techniques in animal studies. They found that isotopic radiocardiography yields an accurate and reproducible measurement of the time it takes blood to circulate through the lungs, and the volume of blood circulating in the lungs.

Pulmonary arterial volume (PAV) was measured at the VA Hospital, New York, N.Y., by injecting the radioisotope ^{131} I-labeled macroaggregated albumin into the pulmonary arteries of an animal and tracing it through the lungs. It compared with Technetium-99m, another isotope commonly used, with little or no advantage for either.

Pulmonary embolism

Although pulmonary embolism (PE) already is responsible for 50,000 deaths each year, the annual incidence in the U.S. continues to rise, mostly because of larger numbers of elderly people, more extensive surgery, and increased diagnostic sophistication, according to VA investigators at the VA Hopsital, Martinez, Calif. Nevertheless, premortem diagnosis of pulmonary embolism is made in only 10 percent of the cases of those who die as a result of it. Investigations show that medical disorders are the most common cause of PE. Congestive heart failure or atrial fibrillation increase the incidence ten-fold. Deep venous thrombosis, pulmonary disease, and cancer, particularly carcinoma of the prostate, ar high risks. Most important in management of PE, they report, is prevention of venous thrombosis. Recently preoperative anticoagulation has been advocated to prevent postoperative emboli.

A VA investigator at West Roxbury, Mass. reports an estimate of 570,000 patients suffering non-fatal PE in the U.S. annually and 140,000 PE fatalities. Plain chest X-ray is not universally appreciated, but a recent study shows a high diaphragm on the side where the embolism is located. Perfusion lung-scanning should be performed immediately. The literature gives ample evidence of underdiagnosis. The possibility of PE should be suspected more often then it is, the investigator suggests, and multiple-view lung-scanning should be performed in all patients suspected of possible PE. Unless angiography is performed, he states, evaluation for PE without lung-scanning should be considered incomplete.

Bronchodilators

Investigators at the VA Hospital, Memphis, Tenn. demonstrated with animal models that adrenaline, a beta adrenergic agent, produced a rapid increase in cyclic AMP. Isoprenaline was more stimulatory than adrenaline, noradrenaline was less stimulatory, and ephedrine produces a negligible effect. Caffeine and theophylline, methylxanthines, produced an increase in cyclic AMP concentration. Of these, caffeine was the most potent. It is likely that many of the beneficial

effects of these drugs in pulmonary patients occur through similar changes and modulations of the cyclic AMP system.

Investigators at the VA Hopsital, Albuquerque, New Mex. developed a high-pressure liquid chromatographic system to determine the presence of theophylline and its metabolites in human urine.

The recently isolated vasoactive intestinal peptide (VIP), as mentioned previously, has a wide range of biological actions, including vasodilation, hypotension, relaxation of isolated trachea and other smooth muscle organs, and stimulation of cyclic AMP production. VA investigators at Dallas, Texas demonstrated that in animal models the administration of VIP by aerosol affords good protection against bronchial and alveolar-duct constriction due to histamine or other factors. Protection by VIP was maximal after 1 hour and partial protection lasted at least 3 hours. VIP caused no change in heart rate or blood pressure.

Pathophysiology of lung disease

Investigators at the VA Hospital, Indianapolis, Ind. studied oxygen transport during acute alkalosis and abnormally high concentration of inorganic phosphates in the blood. They found that hyperventilated animals, whether infused with inorganic phosphates or not, had decreases in cardiac output and increases in the volume of oxygen in their lung tissue.

At Wood, Wisc., VA investigators made an electron microscope study of lung tissue of a patient with extensive fibrosis in both lungs. They identified particles of cobalt, iron, chromium and nickel, and implicated cobalt as a possible cause of interstitial pneumonitis-fibrosis in industrial workers.

At the VA Hospital, Little Rock, Ark., investigators studied enlargement of the heart in patients with chronic bronchitis and emphysema. Among 72 patients, they found 20 (78 percent) had enlarged left ventricles and that half of these had high blood pressure or arteriosclerotic heart disease, or both.

In a study of electrocardiographic diagnosis of enlargement of the right ventricle of the heart, which pumps blood to the lungs, in chronic obstructive pulmonary disease, investigators at the same VA hospital found that of 71 patients, 30 had definite, and 3 had probable enlargement of the right ventricle, and 18 patients had enlargement of the left ventricle. They found four criteria most reliable for analysis of ventricular enlargement and report that these critieria may be used effectively in predicting enlargement of the right ventricle of the heart in chronic obstructive pulmonary disease.

In a study of allografted lungs in matched animals with induced pulmonary hypertension, medical investigators at the Oklahoma City, Okla. VA Hospital found that pathological symptoms developed similar to the phenomena of chronically rejected renal allografts.

Although constituents of marijuana have been identified and the physiological effects of tetrahydrocannabinol have been demonstrated (marijuana frequently contains cannabinol), VA investigators at Indianapolis, Ind. studied its effects on animals. They found that animals treated with cannabinol showed a trend toward increase heart rate and decreased cardiac output.

Social sciences

Social science research in the VA is clinical and intended to improve patient care. Some studies deal with the social functioning of VA patients in the hospital or community and with the evaluation of programs designed to enhance adjustment. Others concern psychosocial factors and their relationship to illness.

Determining readiness for the discharge of psychiatric patients is difficult. At the VA Hospital, Waco, Texas, the Social Adequacy Rating Scale (SARS) is being developed to quantify eight areas of social adjustment. The brief scale was used to evaluate all psychiatric patients who were hospitalized more than six months and correlated significantly with a longer scale, which measured discharge readiness. The SARS was recommended as a means for detecting patients for return to the community.

Once patients are identified as ready for discharge, the type of aftercare must be selected. Five studies have dealt with evaluating outplacement facilities and the quality of care. The effect of age on the outcome of foster care placement was examined with 572 male psychiatric patients due to be discharged from 5 VA hospitals. The men were assigned randomly to foster care preparation and placement or to continued hospitalization and were studied for one year. About 73 percent of both older and younger patients were actually placed in foster care and they functioned and adjusted better than those who remained in the hospital. Only 14 percent were over age 60. Older patients responded slightly better to preparation than younger ones and older patients adjusted as well as younger ones in the community, with about the same return rate to the hospital. Foster care seems appropriate and probably underutilized by psychiatric hospitals for their elderly patients.

In Miami, Fla., 1000 patients in community nursing homes were studied at the time of placement when the levels of disability, impairment, prognoses, and demographic variables were determined. Nursing homes were measured on a 71-item scale providing scores for meals, services, policies, plant, records, and safety. Data were also collected on staffing hours, costs, and turnover rates. Patients were re-evaluated at six months and classified as living or dead; improved, unchanged or deteriorated; and discharged, still in the home, or readmitted to the hospital. The only variable consistently related to outcome was the number of professional nursing hours, a finding compatible with other studies where structural variables seldom predict the quality of care. Apparently the only way to improve the outcome is to increase the professional nursing hours.

In the same Miami VA study ratings of 6 social workers with knowledge of the nursing homes agreed closely when they ranked 40 facilities on a 5-point scale ranging from high to low quality. To determine the relationship of their opinion to more standardized assessments, researchers without prior knowledge of the homes rated them on a 90-item scale. The two sources of data correlated well, suggesting that expert opinion could substitute for more costly first-hand assessments by visits.

To alleviate critical housing needs of the elderly, consideration has been given to the use of vacated college dormitories but little research

has been done on the few intergenerational living complexes which exist. At the VA Hospital, Bath, N.Y., a sociologist reviewed attempts to use dormitories as housing for the elderly and warned that there are problems of isolation and undesirable architectural features.

A controlled study of a volunteer program called Project Anchor was conducted in three VA hospitals. Volunteers helped recently released mental patients to become reintegrated into the community. Eighty-nine patients were randomly assigned to 78 volunteers, and 82 patients to an unaided control group. Data from interviews, questionnaires and records showed little therapeutic effect of the volunteers. The results question the uncritical use or funds and personnel for outpatient volunteer programs.

VA staff are particularly concerned about social disability resulting from alcohol and drug abuse. In a suburban area of Los Angeles, Calif., a VA social worker collaborated with the medical school in a study of 74 high school students. Students' drug use, attitudes and behavior were measured. About half had used drugs in the previous year but none heavily. The youths resembled heavy drug users attending free clinics except in their attitudes and life style. The heavy users were more like sterotypes of "hang-loose hippies."

Also, at the VA Hospital, Houston, Texas, patients in two 60-day treatment programs for alcoholism were studied up to one year after discharge. The more traditional treatment such as psychotherapy produced less favorable results than the experimental ward-oriented treatment and patients receiving psychotherapy were slightly more disturbed.

At the VA Hospital, Topeka, Kans., a clinical program for treating chemically dependent veterans involves five hours a week of alpha-theta training over a five-week period with ancillary programs of meditative and reverie states used as a problem-solving device. Psychological testing before and after treatment of 60 patients compared with controls showed significant trends toward a less depressive effect, improved impulse control, increased sensitivity to ones' own needs and feelings, and greater ability to handle aggressive feelings.

In Miami, preliminary work on a project jointly funded by the National Institute of Drug Abuse and VA showed that 30 percent of patients left treatment in alcohol units and 25 percent in drug units. Dropouts tended to be older, fewer were married, and they had used drugs longer than those who continued treatment. Admission data on mood, attitudes, social functioning, and perception of the ward showed no difference between completers and dropouts. The initial levels of motivation and staff opinion about the need for hospitalization significantly identified dropouts.

VA concern with social issues, such as increased violence, is demonstrated by two studies. From the VA Hospital, Cincinnati, Ohio, 148 mental health workers were surveyed to determine how many patients seen in the previous year posed physical threats to others or to the therapist and how many had actually assaulted the therapist. Of 6,720 patients, 9 percent presented assaultive threats to others, 2 percent to the therapist, and less than 1 percent actually assaulted the therapist. The rate was unrelated to the status of therapist as resident, student, or staff member. Eight general approaches to coping with

assaultive behavior were identified, all reducible to biological, psychological, and social influence.

At the VA Hospital, Perry Point, Md., domestic relations offenders in the state of Maryland were found to be significantly older, more passive in using services, less violent in criminal offenses, possessed of more military service and more dishonorable discharges, and more likely to be working at the time of incarceration than were other prisoners. Both correction and public welfare agencies appeared unsuccessful in coping with these domestic offenders.

Two projects exemplify VA research which relates to family health. Life events, emotional trauma, and social problems have been cited as influencing the outcome of pregnancy. Investigators at the VA Hospital, Seattle, Wash., in conjunction with the university hospital, compared 23 post-partum mothers who delivered prematurely with 23 full-term mothers of matching background. A Schedule of Recent Experience which estimates how much a person's life has changed during a limited period was used to assess events during the pregnancy. Although the two groups reported about as much change, a clustering of such changes seemed to increase medical difficulties during pregnancy, and over 50 percent of the medical difficulties influenced the early onset of labor.

The children of patients were added to part of the treatment program by the Renal Staff at the VA Hospital, Lexington, Ky. They had previously added wives of renal dialysis patients. Evaluation of the program led the staff to recommend working with the children of dialysis patients as a part of improving the total family functioning.

VA's mission includes the education of health professionals. In an attempt to determine what criteria should select entrants to social work education, 58 entering graduate students were tested on attitudes concerning dogmatism, authoritarianism, and alienation, as well as IQ, and data were recorded on grade point averages and undergraduate majors. At the end of the academic year, the faculty on the one hand and field instructors on the other rated overall performance of the students. Attitudinal scales predicted faculty but not field instructors' ratings suggesting that field instructors should be more involved in selecting students and that schools should seek new screening devices.

Spinal cord disorders

The widening interest in spinal cord injury research covers all aspects of care. Research efforts have emphasized basic scientific aspects of early and continuing care of spinal cord injuries as well as determining the community's needs for treatment facilities.

Spasticity has been and remains a major problem in the rehabilitation of spinal cord injury patients and many studies have been devoted to defining the effects of the antispastic agent, Lioresal. Data obtained in the isolated frog spinal cord suggest that Lioresal acts essentially presynaptically, possibly by beginning impulse conduction in pre-terminal axons. This mechanism might contribute to its clinical effects in spastic patients. Clinically, another drug, Dantrolene, improves functional abilities in spastic patients without contractures and eliminates painful spasms of the limbs and bladder.

Educational, vocational and psycho-social problems are of major importance in the rehabilitation of spinal cord patients. One study, at the VA Hospital, Memphis, Tenn., has estabilshed the role of the educational, vocational coordinator in the spinal cord injury service. Two other studies from the VA Hospital, Wood, Wisc., have emphasized the thrust of the psycho-ecological approach to environmental factors affecting spinal cord rehabilitation patients. Both studies showed that the psychologist plays an important role in the total rehabilitation of a spinal cord patient.

Spinal cord injury research at the VA Hospital, Madison, Wisc., has involved functional restoration following transection of spinal cord in mammals using grafts of autogenous brain tissue, sciatic nerve and nodose ganglion. Structural continuity was achieved in the animals grafted with autogenous sciatic nerve. At the VA Hospital, Palo Alto, Calif., the neuroglial response following experimental spinal cord transection was examined. In five fish, complete transection was followed by axonal regeneration, while in two fish, stumps failed to reunite. No fibrous gliosis was present in the descending tracts.

At the VA Hospital, West Roxbury, Mass., urodynamics have been extensively studied. The vascular component to intraurethral pressure was found to be small and changes in intraurethral pressure with sympathetic stimulation are mediated through changes in the smooth muscle of the urethra. Bladder filling is accompanied by increased sympathetic activity in the "internal sphincter." Methods of bladder rehabilitation during and after spinal shock were investigated and the technique utilized for monitoring urethrovesical pressures described. It was objectively shown, for the first time, that the external urethral sphincter displays a high resistance during spinal shock.

Impotence is an important problem in patients with spinal cord injury. The VA Hospital, Miami, Fla. reported impotence as a complication of external sphincterotomy—a possible complication well-known in this field. The same group reported their experience with the use of a penile prosthesis for the management of impotence.

Urinary incontinence is of major importance, not only in neurogenic bladder but also in post-prostatectomy patients. The treatment of this condition with electrical stimulation of the pelvic floor was investigated at the VA Hospital, Martinez, Calif. Pelvic floor stimulation succeeded in patients with stress and with congenital, iatrogenic, and postoperative urinary incontinence.

The VA Hospital, New York, N.Y. reported a ten-year experience with colonic urinary diversion in patients with and without neurogenic bladders. Among the advantages of this type of operation are minimal stomal stenosis, little residuum, less electrolyte disturbance and availability for high and low diversion.

The VA Center, Wilmington, Del. reported promising experimental results in urinary stone disintegration utilizing electrohydraulic lithotripsy, a method which has been extensively utilized in Eastern countries.

At the VA Hospital, Seattle, Wash., medical, social and psychological evaluations were made of the value of ileal conduit diversion

in patients with defective development of the spinal cord (myelodysplasia).

Investigators at the VA Hospital, Portland, Oreg. involved the well-known abnormally high potassium content of the blood (hyperkalemia) following succinylcholine utilization in spinal cord injury patients during anesthesia. This complication can be prevented by using non-depolarizing muscle relaxants for patients with denervated skeletal muscle.

In the area of neurosurgery, the VA Hospital, Los Angeles, Calif., reported the development of pseudomeningocele as a cause of progressive myelopathy one of the complications following certain types of spinal surgery. Other causes of neurologic deficit were found to be diverticula of the arachnoid, reported from the VA Hospital, Boston, Mass. and spontaneous spinal epidural hemorrhage as an unusual complication of chronic alcoholism, reported from the VA Hospital, San Diego, Calif. A group in the VA Hospital, Madison, Wisc. showed that a true synovial cyst of the spine can cause pain in the neck.

Investigators at the VA Hospital, Miami, Fla. described improved materials and methods for making transcutaneous stimulation in the treatment of pain. In the VA Hospital, West Roxbury, Mass., a group study reported for the first time in the United States the results of air myelogram in spinal cord injured patients. This examination may be one of the best for visualizing the entire circumference of the spinal cord pointing to the need for an operation.

Problems relating to reconstructing and improving hand function in patients with cervical cord injuries are of great importance. At the VA Hospital, Cleveland, Ohio, careful selection of patients undergoing tendon transfers improved grasping abilities.

In another field, plastic surgery is of great importance and it was shown experimentally in the VA Hospital, New Orleans, La., that it is possible to increase flap survival by means of arterial venous anastomosis. In the same area of skin pathology, investigators at the VA Hospital, Palo Alto, Calif., have been studying wheelchair cushions to try to reduce pressure in the sitting position.

Surgery

Surgical research in the VA includes: (1) *basic science* in which surgeons have conducted research in organ and tissue preservation, immunology of transplantation, neurophysiology, cardiopulmonary physiology and collagen synthesis; (2) *clinical research* with controlled clinical studies of a new physiologic approach and/or new pharmacological adjuncts to existing surgical procedures including cooperative evaluations of immunological adjuncts to cancer surgery, coronary artery bypass surgery, or evaluation of new selective vagotomy procedures for ulcer disease; (3) *the development of new mechanical devices* or operative procedures such as nuclear powered cardiac pacemakers, heart lung machines, artificial lungs or new shunting operations for intractable ascites in collaboration with engineers, physicists and chemists.

During the past year in *basic science research*, significant progress has been made in the biology of wound-healing, especially of trouble-

some tissues such as cartilage. VA investigators at Palo Alto, California and Syracuse, New York demonstrated that electric currents and ionic fields exert a previously unknown but profound effect in the healing of bone and cartilage. New approaches to collagen synthesis were investigated at VA Hospitals in Tucson, Arizona, and Little Rock, Arkansas.

The pathophysiologic events affecting cells, blood elements, and organ respiration were studied to provide basic information for the use of an artificial lung by investigators at the VA Hospital, Bronx, New York. VA investigators at Palo Alto, California are conducting a critical evaluation of myocardial function after ischemic insult. This has added greatly to the practical application of a quiet heart during delicate cardiac surgery. Organ systems are being improved with new knowledge accrued at the molecular and cellular level at Salt Lake City, Utah and Miami, Florida. The use of new oxygen-carrying fluids in the absence of blood has been demonstrated as well as the role of such agents as allopurinol and lysosome stabilizers to prevent cellular deterioration of organs on perfusion and storage for transplantation.

In transplant immunology, the VA Hospital, Minneapolis, Minnesota has made significant progress in the manipulation of lymphocyte function, enhancement of organ grafting such as kidneys and skin and the alteration of tissue immunogenicity. Results of clinical renal transplantation here as well as at Richmond, Virginia have been significantly improved over previous years because of these studies together with the use of newly developed antilymphoblast and antithymocyte globulins. The VA Hospital, Denver, Colorado, continues to collect information on the long-term results of kidney transplantation. One of the original transplant centers, the hospital now has many patients with ten-year survival and functioning grafts and other data on clinical and experimental liver transplantation. The results are constantly improving in this latter complex procedure. Also at Denver, investigators have defined a relationship between cancer and immunosuppression in transplant patients and have established a transplant tumor registry.

The biosynthesis of clot formation, and the prevention of thromboembolism is being investigated at the VA Hospital in Albany, New York. Results of this study suggest that depressed ability to dissolve fibrin, basic to the formation of blood clots and deposits that narrow the channels of circulating blood, and accompanying biochemical changes may predispose patients to become atherosclerotic. In Boston, this has already led to the use of new filter and extraction techniques for pulmonary emboli by non-operative methods. Medical investigators studying animals were able to introduce through a jugular catheter, silastic ballons, dacron covered springs, and umbrella filters to strain out emboli that would otherwise be trapped in the lungs. They found the perforated umbrella filter to be most effective in preventing pulmonary embolism.

Surgical bacteriology is being more fully delineated in host-pathogen and pathogen-pathogen inter-relationships at several VA Hospitals. At Madison, Wis., a self-administered dip-strip device is reported to be used satisfactorily by the patients themselves to screen

for urinary tract infection—and the bacteria that cause it—in female subjects. At Miami, Fla., the varying sensitivity of micro-organisms to anti-bacterial agents (drugs) was studied in pure vs. mixed cultures. They found that organisms growing in mixed cultures showed decreased sensitivity to the drugs in 30 percent of cultures and total obliteration of sensitivity occurring 10 percent of the time. They suggest that both pure and mixed culture sensitivity be done for all mixed infections, since this more clearly represents the clinical picture. At Hines, Ill., a special relationship of gastric procedures to the development of new pathogenic bacterial flora has been shown.

In *clinical studies*, the treatment of cancer using new immune adjuvants such as Bacillus Calmette Guerin (BCG) is being evaluated at several VA centers including St. Louis, Mo., where investigators reported that uveitis and vitiligo were associated with BCG treatment of two patients for malignant melanoma. Both patients are living and well after 33 and 32 months of nonspecific immunotherapy. To explain this unusual response to treatment, they suggest BCG (and possibly isoniazid) may be able to foster a cytotoxic auto-immune reaction—in which the patient's own immune system attacks his own melanin-producing cells (pigment producing) in certain patients with melanoma.

VA investigators at Los Angeles, Calif. began with the knowledge that, despite surgery, about four of five patients with malignant melanoma metastasis, or spread to lymph nodes, succumb to this metastasis of their cancer. They found that treating these patients with BCG as well as surgery reduced the incidence of metastasis after two years to half that of those treated by surgery alone; even when metastasis occurred in BCG patients it was delayed six months. Ninety percent of BCG patients with microscopic metastasis in one node, remained free of the disease compared to 40 percent of those who had larger tumors in multiple nodes. They suggest BCG has an inhibiting effect on "micrometastases" of malignant melanoma. The study of gastric function at new molecular and subcellular levels as well as in the controlled clinical multi-institutional evaluation of operative procedures such as selective vagotomy, vagotomy and pyloroplasty and antrectomy is yielding definitive answers to the old surgical questions of dumping syndrome vs. recurrence rates and as to which patients should have which operations. A VA study at Houston, Texas was a prospective evaluation of vagotomy-pyloroplasty vs. vagotomy-antrectomy surgical procedures for treatment of duodenal ulcers. With a 5- to 8-year followup on 200 operations, the Chief Surgeon at the Houston VA Hospital concludes that vagotomy-antrectomy is the superior procedure for most patients because it is associated with fewer recurrent ulcers without a significant difference in the severity of other postoperative gastrointestinal complaints.

The closer metabolic study of obesity and objective clinical trials of jejuno-ileal bypass surgery is beginning at VA Hospitals in Los Angeles, Calif., Syracuse, N.Y., and Baltimore, Md.

New approaches to anesthesia using scientifically validated modifications of acupuncture and electroanesthesia are being initiated at the VA Hospital in Gainesville, Fla. Here investigators performed 979 acupuncture treatments in 261 patients with chronic pain. A substantial number of the patients stated that they had relief immedi-

ately following a series of four acupuncture treatments. It did not matter whether the needles were placed in the traditional meridian locations or in arbitrary fixed control points. Four weeks after treatment, 65 percent of the patients reported little or no reduction in the intensity of their pain, 17 percent reported a 50 percent reduction and 18 percent reported at least a 75 percent reduction in their pain.

Also, the use of new inhalation anesthetic agents with significantly less renal and hepatic toxicity have been initiated at a number of VA hospitals. In a study of the metabolism of enflurane, isoflurane, and methoxyflurane, VA investigators at Palo Alto, Calif. found that solubility of the anesthetic in the tissues is the most important influence in the readiness with which these anesthetics are metabolized. All three are metabolized in vivo—in the living body—to inorganic fluoride, by the stimulation from the enzyme fluorinase. Enzyme induction with phenobarbitol in rats enhances defluorination of methoxyflurane but does not enhance defluorination of enflurane or isoflurane. The fact that the latter are 5 to 10 times less soluble in most tissues, including fat, than is methoxyflurane, is believed to explain the difference.

Palo Alto VA investigators also report that clinical neuroscientists are intensely interested in cerebral blood flow and metabolism because of two independent advances: (1) Recognition that cerebral blood flow is not uniform throughout the brain, and regulation of blood flow to areas known to lack normal blood supply may be lost or may be different from that prevailing in the normal brain, (2) the technique of measuring cerebral blood flow in different regions of the brain. Of several, the greatest clinical applicability involves the injection of a diffusible isotope (radioactive substance which may be traced) into a carotid artery which supplies the brain, and the subsequent measurement of the rate of decay of isotope's radioactivity by collimator probes placed about the head. These probes may be focused on desired cross-sectional planes within the brain. While relatively simple to operate the equipment is not yet readily available because of its high cost.

The choroid plexus and its role in the elaboration of cerebrospinal fluid (CSF) are highlighted in a study of cerebral circulation at the Albuquerque, N. Mex., VA Hospital. This VA investigator reports that major interest in the choroid pleuxs has centered around its role of primary responsibility for the secretion of CSF. The most important finding, however, has been the proven ability of choroid plexus tissue to bidirectionally transport a number of biologically important substances. He suggests that the choroid plexus acts as a miniature kidney and together with the blood-brain barrier regulates the environment of brain cells.

Medical investigators at the VA Hospital, Washington, D.C. studied the interaction of gallamine and pancuronium with tubocurarine, a neuromuscular blocking agent, in morphine-nitrous oxide anesthesia. They found that gallamine gave the fastest onset of anesthesia and that curonium appeared to be six to seven times as potent as tubocurarine at the above-average dosage levels. Both the magnitude and duration of the action of both drugs were significantly greater after prior administration of tubocurarine.

A new method using short-acting hypotensive anesthesia is being evaluated presently at the VA Hospital, Houston, Texas for critical neurosurgical procedures. Transport mechanisms of the choroid plexus are being investigated for the evaluation of cerebrospinal fluid mechanics and function for the treatment of hydrocephalus.

Coronary artery bypass is being prospectively and objectively evaluated for the treatment of angina pectoris and for the prolongation of life in cardiac patients at several VA hospitals.

The dissolution of gallstones by purely medical treatment with bile salts and fat solute emulsifiers is being tested by the group at Salt Lake City, Utah. They found that the best combination among fat solute emulsifiers was equal parts of unconjugated deoxycholate with lethicin solution with the individual bile salts in physiological concentration.

In the use of applied mechanical devices, new electronic pacemakers for the bladder in veteran paraplegics at Boston, Mass. and Minneapolis, Minn. are being tested. The Minneapolis surgeons report the successful implantation of a Mentor bladder stimulator and a pelvic floor stimulator in each of two patients with urinary incontinence and chronic urinary tract infection due to meningomyelocele. Electric stimulation emptied the bladders of both patients with low residual urine in each case. One patient has sterile urine off medication and the other patient's urinary infection is easily controlled with medication. Studies in cardiac pacemakers are continuing to progress with thermopile nuclear implantable devices as well as new concepts in the maintenance of cardiac function. The experience of two years by surgeons at the VA Hospital, Buffalo, N.Y. coincides with a worldwide experience of nearly four years indicating a high degree of reliability in an atomic pacemaker—the Metronomic-Laurens-Alcatel isotopic cardiac pacemaker. Performance data indicate a potential pulse generator life of 20 years for the pacemaker. Less expensive, non-nuclear power sources can be expected to satisfy the five-to-ten-year requirements of 85 percent of the patients requiring a pacemaker.

Also, a pulsatile intra-aorta balloon counterpulsation for cardiac resusitation is being studied as a cardiac assist device which is practical now for clinical use. Surgeons at the Denver, Colo. VA Hospital report a simple, safe and effective method of producing pulsatile flow during cardiopulmonary bypass surgery. They have used intra-aortic balloon pumping (IAMP) in 56 patients with no complications ensuing.

An ingenious, simple, new shunt operation is being evaluated for the treatment of intractable ascites using a new implantable valve at the VA Hospital, Brooklyn, N.Y. and other VA centers. The procedure consists of a minor surgical operation for ascites, wherein a specially designed one-way pressure activated valve is implanted to create a permanent peritoneo-venous shunt.

In conclusion, the VA system represents leading research in surgery that continues to add to medical progress as a spin-off to many areas in basic as well as clinical research, in addition to producing advances in specific surgical problems.

Vision

In 1975 the National Advisory Eye Council identified five major visual problems: cataract, retinal and choroidal disease, glaucoma, corneal disease, and sensory and motor disorders. Research in VA hospitals includes investigations in each of these major problem areas as well as in an area unique to the VA; that of blind rehabilitation. VA research pioneered the development of prosthetic devices to assist blind patients, including a laser cane.

Investigators at the VA Hospital, Washington, D.C. studied the difference in the adhesion between retinal layers in the light- and dark-adapted state in experimental animals. This information is of benefit in the treatment of patients with detachment of the retina. At the VA Hospital, Wood, Wis., pioneering work was done on the cornea of the human eye including experiments on animals eyes and on ways to improve the preservation of eyes for corneal transplantation. In comparing serum-versus eye-bank-storage of animal corneas, they found that the endothelial cells remained viable longer in the eye-bank-stored corneas than in the serum-stored corneas. They also studied the effect of tranquilizing medication on the vision, a particularly important problem in the VA with the many neuropsychiatric patients receiving these drugs.

Investigators at the VA Hospital, Gainesville, Fla., have studied the basic mechanism of protein movement within the optic nerve in hopes of gaining a better understanding of the disease glaucoma.

Researchers at the VA Hospital, Miami, Fla. have studied eye movements in order to understand better the sensory and motor disorders of the eye. Recent expansion in the use of eye movement recording techniques is providing evidence of ocular motor system dysfunction heretofore evaluated only by clinical observation. These investigators have found that pathologically slow segmental velocities in eye movement occurred only in patients with neurologic diseases such as dystrophy, atrophy and palsy. The method may become a useful tool in the diagnosis of the pathologic state.

Other investigators at the same hospital have studied the blood flow in experimental animals as it varies with the amount of oxygen the animal received—a study important in the understanding of visual mechanisms and the care of patients. In another study, using monkeys, a gas (sulfur hexafluoride) has been applied in the attachment of the retina. The fact that the gas remains in the eye twice as long as air, has allowed sufficient time for the retina to develop a firm adhesion to the treated choroid and pigment epithelium. No toxic effects were observed.

Vitrectomy, which is the removal of the vitreous jelly within the interior of the eye under microscopic control with very fine specific instruments, was pioneered at the Miami VA Hospital.

Studies at the VA Hospital, Sepulveda, Calif. have produced biochemical information in the understanding of the cells of vision in the retina of experimental animals. Researchers at the VA Hospital, Boston, Mass. have reported on the effect of agents used to reduce inflammation of a specific layer in animal eyes. This type of research

is helpful in understanding ways of combating inflammation within the eye.

Investigators at the VA Hospital, Little Rock, Ark. reported on changes within animal eyes when they were treated with laser beams. Pressure measurements are important in understanding potential hazards of laser treatment and a better understanding of their mechanisms.

Work at the VA Hospital, San Francisco, Calif. provided insight into a possible mechanism of visual decrease following the treatment of glaucoma in patients who have had cataract surgery. At the same hospital, investigators have developed a more organized way of protecting delicate instruments used in eye surgery and have pointed out the hazard of all aluminum cans in causing eye injuries. At the VA Hospital, San Diego, Calif., new ways have been developed to study the pressure in the eye in hopes of better understanding glaucoma as well as studying a comparison between the eyes of animals and humans. The same investigators reported the effect of a new technique for cataract extraction on the cornea and a better understanding of possible complications and ways of preventing them.

MULTI-HOSPITAL RESEARCH

Cooperative studies

Cooperative studies are those joint programs in which investigators from different VA field stations agree to study collectively any selected problem in a uniform manner with identical records and a single group report. Cooperative studies are uniquely appropriate to the VA because they make use of the largest volume of clinical material under the auspices of any single agency. The device of cooperative studies is available to investigators who wish to use it to answer appropriate questions in clinical areas.

The VA is a part of the general United States health care system involving both the Federal government and the public. Public Law 89–785, passed in November 1966, indicated that the VA is a part of the community and is to share with and be shared by the community. This is one fundamental principle upon which VA conducts the various cooperative clinical studies described below. A list of the participants in these studies appears in Part II, Data Supplement.

Cooperative studies in cancer

1. *Lung cancer theory*

This cooperative study group, formed in 1957 and begun in 1958, currently has 18 participating VA hospitals. Over 9,000 patients have been studied in thirteen controlled clinical trials under the principal investigators in VA hospitals. A pathology panel of three distinguished pathologists reviews and classifies all histologic material.

Current studies

The fourteenth study compares three drug combinations: cyclophosphamide plus CCNU, cyclophosphamide plus adriamycin, and CCNU plus adriamycin. If the disease progresses, treatment is

changed to one of the other two combinations. Patients are stratified by performance status, prior therapy and measurable diseases; the results are analyzed using these variables and cell type. Therapeutic effect is measured by survival, changes in size of measurable and evaluable lesions, and occurrence, if any, of new metastatic disease. Approximately 332 patients will enter this study before it is completed during fiscal year 1976.

The fifteenth study involves patients with limited disease whereas the fourteenth is confined to extensive disease patients. The fifteenth study compares short courses versus long courses of irradiation with and without low dose prophylactic irradiation to the brain. Results will be evaluated on the basis of long-term survival, relapse-free period and tumor response. The 240 patients needed to detect a 50 percent increase in relapse-free survival will be studied in the 18 months after March 1975, when the work began.

Accomplishments to date include: (a) validation of the World Health Organization classification of cell typing; (b) determination that extent of disease, cell type and initial performance status are factors in determining survival and perhaps response to treatment; (c) demonstration that cyclophosphamide in extensive disease and radiotherapy in limited disease give better survival than placebo; (d) evidence in the thirteenth trial that CCNU plus cyclophosphamide appears to have a slight advantage over cyclophosphamide alone; (e) demonstration in the current fourteenth study appears that adriamycin in combination with either cyclophosphamide or CCNU has a beneficial effect on squamous and poorly differentiated squamous cell types; and (f) development of a method of predicting survival based on the demonstrated important predictor variables so that fewer patients may be needed to assess new therapeutic regimens.

2. *Surgical adjuvant cancer therapy*

The activities of the VA Surgical Adjuvant Cancer Therapy Group have continued during the past year with accrual of patients in five separate studies. In addition, followup of all patients remaining in previous protocols has continued. Membership in the group was adjusted during the past year. Two members withdrew, three new members were added and two additional hospitals are probational.

The present status of the work is as follows: Total number of patients screened—27,115; total entered into studies—9,231; entered during past year—477; total living patients under observation—1,815; and total patients living more than 5 years—1,043.

In addition, final observation of the ten-year followup of the 392 patients with lung cancer in the VA-Armed Services Solitary Pulmonary Nodule Study was completed.

Ongoing trials

1. *Lung.*—For this trial a combination of CCNU and Hydroxyurea, both given orally, has been used. A total of 262 patients have been entered into this study, 170 during the past year. Plans are now underway for use of a different drug regimen, possibly incorporating MER.

2. *Colon.*—A combination of Methyl CCNU and 5-FU is used for patients randomized to receive the drug in this trial. A total of 235 patients has been entered, 152 during the past year.

3. *Rectum.*—Patients with low-lying lesions with planned abdomino-perineal resection are randomized to receive preoperative radiotherapy. Ninety-two patients have been entered into this study, 60 during the past year.

4. *Stomach.*—A combination of Methyl CCNU and 5-FU is used in this trial which began in the latter part of 1974. Only 31 patients have been entered thus far.

5. *Pancreas.*—A combination of CCNU and 5-FU is used for patients in this study. One hundred fifteen patients have been entered thus far, 64 during the past year.

3. *Urological research group*

The Prostate and Bladder Studies continued admitting patients. However, no analyses of the results are available to support statements at this time.

The Prostate Study III is treating early cancer of the prostate with radical prostatectomy plus placebo or placebo alone. Advanced prostatic cancer is being treated by Premarin, Provera, stilbestrol, and stilbestrol plus Provera.

The Bladder Study II has been treating early cancer of the bladder with transurethral resection of the bladder with the addition of topical thio-TEPA, oral pyridoxine, or placebo.

When data from these studies have been processed, a report of the findings will be published.

4. *Brain tumor cooperative group*

Five VA hospitals are participating in the Brain Tumor Study Group: San Francisco, Calif.; Durham, N.C.; Indianapolis, Ind.; New York, N.Y.; and Lexington, Ky.

The total of 107 patients randomized for treatment in these 5 hospitals in the late stages of the study compares favorably with the numbers submitted by other non-VA participating institutions. These patients were distributed equally for treatment of malignant astrocytomas with: (1) Methyl CCNU; (2) radiation therapy; (3) BCNU and irradiation; and (4) Methyl CCNU and irradiation.

Results of the study to date are comparable to the results of the previous late stages. Survival is best among the patients treated with a combination of BCNU or Methyl CCNU and irradiation. The next best survival is among patients treated with radiation alone and the shortest survival is among patients treated with Methyl CCNU alone.

An earlier stage involved evaluation of patients with malignant brain tumors. Half of these patients were randomized for treatment with Streptozotocin; the other half were randomized for treatment with Adriamycin. Increasingly, patients are referred for treatment to the study from other VA hospitals.

Only preliminary data representing patients randomized are available for analysis at this time. The maximum response rate for Streptozotocin is 25 percent; for Adriamycin it is 30 percent. While the response rates of these two drugs compare unfavorably with that of BCNU (63 percent), they compare more favorably with the rate of 37 percent for CCNU and 48 percent for Procarbazine. The data are preliminary and require correlation with the national figures, a process now underway in the Brain Tumor Study Group Central Office.

Computerized tomography (CT Scan) has been available for a year and a half and has proven useful in the diagnosis, evaluation and management of patients with malignant brain tumors. A study is in progress to determine whether the CT Scan will prove useful in predicting tumor recurrence.

5. ***Radiotherapy versus surgery or delayed hormonal therapy in treatment of prostatic carcinoma***

This study on the evaluation of radiotherapy in the management of prostatic carcinoma was begun in the previous fiscal year. The prime goal of the study is to determine the effect of radiotherapy versus delayed endocrine therapy in the management of nonsurgical (inoperable) prostatic adenocarcinoma and to evaluate the role of radiotherapy versus radical prostatectomy in the management of surgically excisable prostatic adenocarcinoma. Simultaneously, the staging benefits of radioisotope bonescanning, pedal lymphangiography and pelvic lymph node sampling are being determined.

Cooperative studies in internal medicine

1. ***Antihypertensive agents***

Study 6.—During the past fiscal year, recruitment of patients continued and as of December 31, 1975, 451 patients had been randomized. A decision was made by the Operations Committee to discontinue randomization since a sufficient number of patients had been obtained. The study is designed to compare the efficacy of propranolol alone and in combination with other antihypertensive agents; namely, hydralazine and hydrochlorothiazide, with the know effective regimen of reserpine and hydrochlorothiazide.

Patient-care personnel at each participating hospital have been trained at the VA Hospital, Washington, D.C., in the fundamentals of hypertensive disease—its treatment, morbidity, etc. They have been trained to supervise the Hypertension Clinic at their facility under the guidance of a staff physician, and in the methods of recording certain technical data such as ECG's, phonocardiograms, and carotid pulse tracings, which are essential to the study.

Patient intake and followup has been completed; data analysis is underway and results will be prepared for publication in the next fiscal year.

Study 7.—This is an investigation of Bethanidine, a drug claimed to offer several advantages over those currently available in the treatment of moderate to severe hypertension. It is a double-blind outpatient trial to compare Bethanidine with Guanethidine in patients with an average diastolic pressure of 100-124 mm Hg while on Hydrochlorothiazide. It is expected that this study will help to define the relative advantages of the two drugs in the management of the more severe forms of hypertension.

The recruitment of patients was terminated a year ago. Slightly more than half of the projected sample size was obtained. This will enable analysis of data at a slightly lower level of discrimination than was initially planned; however, the data will still yield information of considerable clinical importance. The monitoring of observations was continued until the end of the fiscal year, enabling all patients who stayed on treatment to complete at least six months of followup.

The results will be analyzed during the next fiscal year, and a publication prepared.

Study 8.—This study is a sequel to the previous VA Cooperative Studies on Antihypertensive Agents which demonstrated that treating men with diastolic pressures in the range of 105 to 115 mm Hg markedly reduced the major complications of hypertension (JAMA, August 17, 1970).

This trial, funded jointly by the National Heart and Lung Institute and the VA, began in November 1973 in four hospitals, and randomization of subjects terminated this year. The trial was designed to test the feasibility of enrolling and following relatively young Americans (25 to 50 years of age) with mild and uncomplicated hypertension (diastolic pressures of 85 to 105 mm Hg).

It is hoped that the information will be useful in planning and implementing a successful full-scale study designed to determine whether treating mild uncomplicated hypertension will reduce heart attacks and strokes, and at the same time to define the price in terms of side effects which are always associated with therapy.

2. *Hepatitis*

Posttransfusion hepatitis I and II.—The VA has been conducting a series of cooperative studies designed to evaluate the efficacy of various forms of gamma globulin as prophylactic agents against hepatitis. The first of these, an evaluation of posttransfusion hepatitis, was initiated in January 1969 and completed in February 1973. In that study, conventional gamma globulin was compared, using a double-blind, randomized method, with an albumin placebo in 2204 patients.

With the demonstration that almost one-fourth of the cases of hepatitis which developed were of viral B origin, i.e., positive for the hepatitis B surface antigen (HBsAg, Australia Antigen), it was elected to repeat the study and compare the effectiveness of hepatitis B immune serum globulin (HBIG, containing antibodies against viral B hepatitis) with the original gamma globulin. This study has just accepted its last patient (a total of 1000 patients). A 6-months followup period is required for final analysis of the results.

Needlestick hepatitis.—The hyperimmune gamma globulin is also being evaluated in the setting of accidental exposure, by a needlestick or by ingestion, to material infectious for viral B hepatitis. This study includes primarily medical and paramedical personnel. The study terminated this year with the accession of 553 patients.

Over 100,000 specimens of serum have been collected in all three studies and stored in deep freeze for additional serological studies. The studies evaluating HBIG are being conducted in collaboration with the National Institute of Allergy and Infectious Diaseses.

Hepatitis in drug abuses.—A collaborative study has been conducted in three VA hospitals to investigate nonsymptomatic parenteral narcotic addicts for evidence of hepatic disease. This study was terminated this year with almost 600 patients having been entered. A large number of biochemical, serologic and immunologic tests are being evaluated at regular intervals. Liver biopsies are performed if specific abnormalities are detected for a defined period of time. Almost 90 percent of the patients have demonstrated at one time or another, evidence of past or present viral B hepatitis or other liver disease, primarily

alcoholic in origin. Continued followup and additional testing of the specimens of stored sera is in progress.

3. *Crohn's disease*

The National Cooperative Crohn's Disease Study continued intake and followup of patients; 548 patients had been entered in the study as of the end of the fiscal year. The study, supported by the National Institutes of Health and the VA, tests the therapeutic and prophylactic effectiveness of two agents currently in use (Salazopyrine and Prednisone) and seeks to provide a basis for judging the usefulness of azathioprine in treatment of this disease. Preliminary results are expected during the next fiscal year.

Cooperative studies in mental health and behavioral sciences

1. *Social sciences*

Two cooperative studies are underway. Both are controlled evaluations of outplacement programs for psychiatric patients.

The evaluation of foster care by patient attitude and behavior.—The aim of this study was to determine effectiveness of foster care preparation and placement. 572 subjects from 5 hospitals were randomly assigned to foster care preparation (experimentals) or continued hospitalization (controls). They were studied before assignment, at placement of experimentals, and 4 months later regarding social functioning, mood, activity, and overall adjustment. Hospitals averaged 2 months preparing experimentals, resulting in 73 percent placed in foster care. Data collection on the foster care study has been completed and findings submitted for publication. A one-year followup of the patients will be analysed in the coming year.

The evaluation of day treatment care by patient attitude and behavior.—Intake of subjects in this study ended with 162 patients from 10 VA centers. The subjects averaged 37–38 years of age, about half had never married, and half listed parents as next of kin. The average number of prior hospitalizations was four and patients averaged 155 days in the hospital during the year preceding their referral to day treatment. The Day Treatment Study completed patient intake this year and a two-year followup remains.

2. *Drug-abuse prevention*

The LAAM-methadone study.—This study is a joint effort by the VA and the White House Special Action Office for Drug Abuse Prevention (SAODAP) to evaluate the relative safety and efficacy of 1-alpha acetyl methadol (LAAM) and methadone. LAAM has clinical effective range of 48–72 hours in contrast to methadone's 24 hours. This could substantially reduce the take-home doses and its consequent street diversion and accidental poisoning. Logistically a three-time-per-week clinic visit schedule vs. daily schedule could also mean a substantial increase in a clinic's treatment capacity. Less frequent medication may also help to de-emphasize the issue of chemicals in the course of rehabilitation.

A secondary goal of the project was to compare two doses of methadone (50 mg vs. 100 mg) for maintenance therapy. Patients were randomly assigned to one of the three study groups viz methadone 50 mg, methadone 100 mg and LAAM 80 mg. The study was double-blind, with a study period of forty weeks for each completer.

Intake of patients began in April 1973 in three pilot hospitals: Sepulveda and Brentwood, California; and St. Louis, Mo. The last patient completed the study in March 1975. A total of 430 patients from twelve VA hospitals participated in the study. Data collection is now complete and detailed analyses are being carried out. One or more manuscripts will be forthcoming.

3. *Characteristics of effective psychiatric programs*

Although treatment teams in psychiatric hospitals introduce the kinds of programs they feel are most effective, very little definitive research has been carried out to identify the characteristics of effective programs.

The primary purpose of this project is to identify the program dimensions characteristic of effective programs. If the therapeutic ingredients of effective psychiatric programs can be identified and verified in a subsequent controlled study, the application of these findings to VA psychiatric hospitals could result in the same kinds of improvements in treatment effectiveness that occurred with the introduction of tranquilizing drugs. The design of the study requires data collection on both program characteristics and program effectiveness from a large number of psychiatric treatment units in VA hospitals.

The pilot study for this project began in February 1975. Data was collected at all hospitals between May and October 1975. Nineteen hospitals are participating in this study. Measures of program effectiveness and program characteristics will be collected on about 100 treatment wards.

Cooperative study in pulmonary diseases

Chemoprophylaxis of tuberculosis

In January 1965, a study was started with the aim to investigate the ability of Isoniazid (INH) to prevent reactivations of pulmonary tuberculosis in patients with the inactive form of this disease. Eleven VA hospitals participated and recruited a total of 7,035 patients for the study.

The patients were randomized into three groups. One group was given INH daily for two years, another group INH for one year and a third group received no INH. Placebos were also used in the double-blind study. The study ran from 1965 to January 1, 1974.

Data analyses are underway and manuscripts will be prepared for publication.

Cooperative study in speech pathology

Treatment of aphasia

The Cooperative Study on the Effects of Speech and Language Therapy on Recovery from Aphasia, initiated in July 1973, is designed to evaluate the efficacy of two different types of treatment for patients who experience speech and language disorders subsequent to sustaining a left hemisphere cerebral vascular accident. Speech Pathologly and Neurology Services in five VA hospitals are participating in the study.

Patients who meet the general criteria for admission to the study are assigned randomly to receive either the traditional treatment or

nontraditional treatment. Patients in the traditional treatment group receive from four to eight hours of individual therapy each week. Patients in the nontraditional treatment group receive from four to eight hours of group therapy each week with no direct manipulation of speech and language. All patients receive other rehabilitative therapy (physical therapy, occupational therapy, etc.) if prescribed by the attending physician.

During the first year of the study, it became evident that study patient intake was a serious problem. During the second year, patient intake has improved dramatically. It was determined that a sufficient number of study patients could be obtained if intake was extended for one additional year. The requested extension was approved. Therefore, it appears an adequate sample of study patients will be obtained to meet the objectives of the study.

Cooperative studies in surgery

1. *Analgesics*

The VA Cooperative Analgesic Study is now in its twelfth year of operation, with five participating hospitals: Boston, Bronx, Los Angeles, Miami, and Palo Alto, the core facility. The aims of the cooperative study are to establish clinically the relative potency and side-effect liability of new and marketed analgesics and sedatives and to refine further the methodology for this type of research.

In this past fiscal year, two analgesic bioassays and three dose-ranging studies were completed.

Bioassays.—(1) Both morphine and codeine have been used for some years in analgesia studies as standard or reference drugs, morphine in parenteral and codeine in oral studies. Since codeine is also frequently used parenterally, we undertook a study to determine the relationship of these two standards to each other when administered parenterally in postoperative pain. Although there was increased response with increased dose for both drugs, the high dose of codeine (60 mg) was less effective than the low dose of morphine (5 mg), so a further study is underway comparing 5 and 10 mg of morphine with 60 and 120 mg of codeine (2) Meperidine is a very widely used analgesic, yet there is still considerable controversy regarding its overall potency relative to morphine and its time course of action. In the second of two studies, we compared 5 and 10 mg of morphine with 37.5 and 75 mg of meperidine (doses commonly used for pain relief) in 117 patients. These doses proved to be equipotent for peak (maximum) analgesia. However, our earlier study showed that for comparable total analgesia (averaged over a time span of 4 hours), higher doses of meperidine (50 and 100 mg) are necessary.

2. *Coronary arterial disease*

The intake of patients into this cooperative study has now been completed. Over 1,000 patients have been entered into this prospective randomized study, designed to answer the question whether aorto-coronary saphenous vein bypass grafting has a beneficial effect on mortality, morbidity, and quality of life. Approximately 500 patients have been randomized into the medical treatment group and 500 into

the surgical treatment group. This type of study had been advocated by most responsible cardiologists and surgeons throughout the country, but it is the only large-scale study of stable angina which has been concluded, and is now in the followup stage.

Data from the study are now undergoing analysis. The following types of analyses are currently underway: analysis of the screening and coronary angiographic log data; review of the coronary arteriograms; review of electrocardiograms, which are being subjected to computer analysis; assessments of quality of life including angina questionnaires, treadmill tests, and morbidity data; review of operative procedures, and assessment of operative morbidity and complications; analysis of the opacification of vein bypass grafts and correlations with the outcome; a study of the previous subset of implant patients; and finally the major analysis of the 1,000 patients, breaking them into various subsets of patients with similar characteristics.

3. *Esophageal and gastric varices*

This year has been spent doing the final analyses of data from the 277 patients, and the analyses for risk factors of the re-bleeders among the 77 patients in the medically randomized group. Some "whys" and "don'ts" for patients who do not re-bleed, and for patients who do re-bleed, and for patients who are treated with portacaval shunt are emerging. It appears that it is possible to identify a potential re-bleeder who should have a portacaval shunt to prevent re-bleeding.

The in-put into the computer of quality-of-life data in the overall study for all patients also has been completed.

4. *Bowel preparation for colon operations*

The purpose of this study is to determine whether giving antibiotics by mouth in addition to routine bowel preparation before operation can reduce the chance of wound infections and mortality in patients undergoing resection of the large bowel. This is a prospective randomized double-blind clinical trial conducted in nine VA hospitals, designed to collect data on approximately 500 patients over a two-year period. Senior surgeons have been selected at each of the nine hospitals to supervise the study and nurse epidemiologists are being selected to carry out the observations in each hospital. In eight of the nine hospitals careful special bacteriology studies will be done of the bowel content, postoperative stools, and any infections to determine if the antibiotics have suppresed dangerous bacteria.

Cooperative study in pathogenic significance of sickle-cell trait

This study, being performed in 13 VA hospitals, was designed to determine whether the frequency of the sickle-cell trait declines in the older age groups and whether the sickle-cell trait in the presence of certain clinical conditions might be a life-endangering risk that increases with age. The hypothesis will be tested that individuals with the sickle-cell trait have greater susceptibility to pulmonary infarctions, pyelonephritis, vascular complications of diabetes and post-operative thrombotic complications.

The study will include approximately 80,000 individuals. The data thus far obtained on approximately 65,000 veterans have been analyzed with regard to the dependence of the frequency of the sickle-cell trait on age. The relationship of the trait to longevity, morbidity and sever-

ity of certain diseases will be investigated during the next year. The risk of deficiency of the red blood cell enzyme Glucose-6-Phosphate Dehydrogenase alone and combined with the sickle-cell trait will be assessed in a similar way.

Cooperative study on aspirin therapy and unstable angina

This is a prospective, randomized, double-blind clinical trial conducted in 11 VA hospitals to determine whether small doses of aspirin can decrease morbidity and mortality in patients with unstable angina.

A pilot activity was conducted to detect and correct problems before official intake began. Experience with these 50 patients demonstrated that the study is logistically feasible and systems for shipping and receiving samples for enzyme analysis and data flow were established. It also demonstrated that there were no problems in obtaining patient consent and no difficulty in eliciting the patient's compliance.

The Central Laboratory is currently running approximately 400 tests (total CPK, LDH, SGOT, CPK, and LDH isoenzymes, and cholesterols) each week. The participating laboratory technicians are trained in the techniques of platelet aggregation and enzyme analysis. Computer analysis of data is in progress. It is planned for the study to continue until the goal of 1480 patients is reached.

Cooperative study in vasodilator therapy of myocardial infarction

Ten hospitals have now been funded for participation in this study. Eight of these are now randomizing patients and two are recruiting personnel and acquiring the necessary equipment. Approximately 40 patients have already been randomized to date.

Cooperative study of quality control of lab data

The accuracy and precision of routine chemistry and hematology determinations were evaluated in 20 highly automated VA hospital laboratories.

In general, the laboratories were found to be performing at the level of "the state of the art" and, more importantly, meeting realistically a criteria for "Medical needs" for most routine tests. Normal value data showed that it is valid to pool normal values from different laboratories when non-random variables, such as different methodology or equipment have been eliminated.

Cooperative study on drugs and sleep

This project began at the start of fiscal year 1975. It is a serial-study project designed to provide a detailed description of the comparative neurophysiological sleep EEG–EOG, subjective, and psychological effects of two sedative hynotics, a benzodiazepine and a barbiturate. The first study aims for standardization of procedures among the three participating laboratories. Each hospital will study six normal men for three consecutive nights each. The second study is designed to allow determination of equivalent drug doses for the two study drugs. In the third and primary study, 60 men with primary insomnia will be evaluated in a 28-day protocol. The protocol includes laboratory

adjustment, baseline, initial placebo, drug and withdrawal placebo conditions. Patients in the five treatment groups will receive a high dose of the benzodiazepine, a low dose of the benzodiazepine, a high dose of the barbiturate, a low dose of the barbiturate, or placebo, respectively, during the drug period.

NAS–NRC FOLLOWUP AGENCY

Studies with the National Academy of Science-National Research Council

The Medical Follow-up Agency is an activity within the Assembly of Life Sciences of the National Academy of Science-National Research Council. The function of the Agency is to help medical investigators to utilize the records systems of the Veterans' Administration and of the Armed Forces in order to facilitate or to accomplish studies in the natural history of disease, prognosis, etiology, therapeutic efficacy, or others to which these records resources may be appropriate.

The Agency was established following World War II. The program was envisioned as having great potential in view of the large size of the military-veteran population, the relatively good documentation of medical and environmental history during wartime, the ease of rep-representation sampling, the extensive programs of veterans' benefits, and the possibility of linking military, Veterans' Administration, and other health records.

The program is guided by an advisory Committee on Epidemiology and Veterans Follow-up Studies. The content of the program, however, at any given time reflects primarily the interests of individual investigators and sponsoring agencies. The costs of the Agency are funded by one or another of these sponsoring agencies, principally the Veterans' Administration and the National Institutes of Health. The Veterans' Administration, the Armed Forces, and the National Personnel Records Center, National Archive Service (GSA) provide essential support by granting access to the records needed for approved projects. The Medical Follow-up Agency of the Assembly provides a statistical and logistic competence for planning specific studies and assisting individual investigators in the conduct of those approved by the Committee and by the agencies whose records are to be used.

Projects that were active during the year ending June 30, 1975 are summarized briefly below. The funding source for each project is also shown. In addition to specific funding, basic support is required for planning new studies, investigating records resources, devising and testing forms and procedures, conducting pilot studies to assess feasibility and costs, developing new computer programs, and maintaining channels of access to the veteran population and its medical experience. Funds for such basic support are provided by the Veterans' Administration and the National Institutes of Health.

Studies active during fiscal year 1975

Survey of mortality of former prisoners of war (Veterans' Administration)

Shortly after World War II, a study was initiated to examine the health of former prisoners of war for evidence of residual impairment.

Subsequently, the study was extended to include men captured during the Korean War.

The mortality experience of former prisoners and groups of controls, traced for 20 years following World War II and for 12 years following the Korean War, has already been described. Men captured in the Pacific in World War II showed evidence of increased mortality during eight years following repatriation, as also did former Korean War prisoners, but no evidence of impaired survival was seen in the European prisoners. These findings were supported by a more recent study of morbidity in which excesses in hospitalizations for both phychiatric and physical illnesses were seen in the two groups of Pacific prisoners, excesses which persisted for eight years and more after repatriation.

Work is currently under way to update the mortality experience. It was intended originally to extend the follow-up through 1973, but preliminary examination of the numbers of additional deaths identified revealed unexplained shortages during the latter part of 1971 and early 1972. The Veterans' Administration file is being corrected and when this work is complete, the prisoner-of-war and control samples will be resubmitted for a mortality update. As a result, it will be possible to extend the mortality analysis to the end of 1975, thereby adding a full ten years of follow-up to the experience reported earlier, completing the mortality follow-up to 30 years for the World War II component and 22 years for the Korean War samples.

Surgical adjuvant cancer chemotherapy study (Veterans' Administration)

This cooperative study group, for which the Medical Follow-up Agency serves as the Statistical Coordinating Center, includes the surgical services of 27 Veterans Administration hospitals, and was organized in 1957 at the request of the National Cancer Institute to determine if certain drugs would improve survival following surgery for cancer. The Agency provides professional statistical support and has responsibility for the statistical aspects of design of the trials, the collection, processing, analysis, and interpretation of data, and executes the functions of receipt, editing, and coding of data.

By 31 March 1975, after nearly 18 years of collaboration, a total of 9,231 patients had been accepted for study, of whom nearly 1,900 are still alive and being followed. Initially, the objective of drug therapy, administered at and immediately following operation, was to prevent the cells released into the circulation at operation from metastasizing, but when the data were analysed it was clear that failure to cure with resection of the gross tumor was due to existing unrecognized distant metastases. Attention has turned to the use of drug therapy, and more recently immunotherapy, to control remote disease not included in the resection while preoperative X-ray therapy has been used to control local spread. There is evidence that this last technique is of some benefit to men with rectosigmoid lesions. Accession of patients into the following trials is continuing or will commence shortly:

(1) Prolonged therapy with CCNU in combination with 5–FU for carcinoma of the pancreas;

(2) Prolonged therapy with CCNU in combination with Hydroxyurea for bronchogenic cancer;

(3a) Prolonged therapy with ME–CCNU in combination with 5–FU following curative resection of the large bowel;

(3b) Immunotherapy with Methanol Extraction Residue of BCG (MER) added to ME–CCNU in combination with 5–FU following a proved incomplete resection of the larger bowel, to be activated in August 1975;

(4) Preoperative X-ray therapy to patients with proven cancer who are candidates for an abdominoperineal resection (second trial);

(5) Prolonged therapy with ME–CCNU in combination with 5–FU for gastric cancer; and

(6) Immunotherapy with Methanol Extraction Residue of BCG (MER), to be activated in August 1975.

A seventh protocol to compare radition therapy with surgery for cancer of the esophagus is nearing final form.

Two fairly extensive analyses of data are made each year for publication as progress reports. Several additional analyses were performed for publication in the medical literature, including:

(1) A ten-year follow-up of patients with asymptomatic solitary nodules;

(2) A major study of stomach cases entered by July 1969 including an intensive search for a treatment benefit, for patterns of recurrence of disease, and for characteristics of patients and disease which are predictive of recurrence;

(3) A re-analysis of the benefits of preoperative X-ray for rectosigmoid cancers, extending complete follow-up to five postrandomization years; and

(4) An analysis of the two colon trials of 5–FU therapy. It appears that survival time may be slightly improved in the patients to whom drug therapy was assigned.

Thirty-year clinical follow-up of selected demyelinating diseases (Veterans' Administration)

The objective of this long-term prospective study of multiple sclerosis is to describe the course of the disease over a period of 25–30 years in a sample of nearly 500 cases originally diagnosed in the U.S. Army during World War II. The probability that men with optic neuritis will progress to MS or to retrobulbar neuritis without MS will also be assessed for a sample of nearly 200 such cases.

The surviving subjects are being examined nationwide by a group of collaborating neurologists and ophthalmologists under the leadership of Dr. John F. Kurtzke of Georgetown University. Costs of the clinical examinations themselves are being defrayed by the Multiple Sclerosis Society.

As of 30 June 1975, after two years of planning and data collection, 370 men had agreed to be examined and examinations had been completed for 221 of these. The third year schedule calls for the completion of all data collection and analysis of results.

Longitudinal study of cardiovascular disease (Veterans' Administration)

Hillman, Levy, White, and Stroud published in 1944 and 1945 a series of papers on blood pressure and hypertension in more than

22,000 Army officers. Their data were obtained from the annual physical examinations which were performed on all officers until, during World War II, the program was discontinued. In these studies, Levy and his associates showed that heart rate, as well as blood pressure, had important predictive value, at least over the short term of a few years, especially when both were elevated, even though only transiently.

The punch cards used by these investigators have been made available to the Medical Follow-up Agency. These cards confirm the data on initial, final, highest, and lowest blood pressures as obtained from the original longitudinal records. Other data, such as height, weight, heart rate, presence of albumin in the urine, etc. are also present on the punch cards.

The present study has the purpose of extending the earlier observations by including an additional 30 years of follow-up for cardiovascular disease mortality. The principal objectives will be to determine the duration of the prognostic significance of the indicators identified by the earlier investigators and to measure the significance for subsequent mortality of blood pressure, heart rate, and ponderal index, individually and in combination.

Mortality information has been obtained from the Veterans' Administration Beneficiary Identification and Records Locator Subsystem (BIRLS). About 6,500 deaths have occurred in the group and cause of death is being coded from death certificates which are now being obtained.

It is expected that the study will be completed during fiscal year 1976.

Microwave cataract screening (Veterans' Administration)

Since there is concern that chronic exposure to microwave radiation may produce cataracts after a long latency period, the feasibility of studying radar repairmen who served on surveillance aircraft is being explored. A simple cataract viewer has been designed by personnel of the New Orleans Veterans' Administration Hospital and Tulane Medical School. Approximately 160 men who served in a Navy aircraft patrol squadron during the Korean War have been selected for a pilot study. One hundred and twenty-four men were located, 60 of these agreed to participate in the study, and 52 examinations have been performed. Approximately one-half of the men have reported findings which are suspicious, and present plans call for referring all who accepted for ophthalmologic examination.

Monitoring records resources (Veterans' Administration)

A routine mortality check of the Twin Registry in BIRLS revealed a dramatic decrease in numbers of deaths reported in 1971 and what appeared to be an under-reporting in 1972. The same condition was found to be present in each roster that had been checked against BIRLS. Subsequent analysis of date of death showed that the under-reporting occurred principally in the last six months of 1971 and possibly the early months of 1972.

Discussions with concerned Veterans' Administration staff revealed that the deficiency was not known to the VA; subsequent consultations with personnel of the BIRLS Systems group resulted in the conclusion that the problem had occurred during the transition period from

manual to computerized operations and could be remedied relatively easily. The Medical Follow-up Agency will resubmit its rosters in the near future.

A potential threat to the use of federal records systems for research purposes was raised by the passage by Congress, in December 1974, of the Privacy Act of 1974, Public Law 93–579. The wording of the law seemed somewhat ambiguous as it applied to the use of records for research purposes; the key would be found in the interpretations made by the Office of Management and Budget. Numerous discussions were held with officials at the various agencies whose records the Medical Follow-up Agency customarily employs and with interested members of committees set up by such organizations as the American Public Health Association and the New England Cancer Society to counter the possible threat to medical research implied by the Act.

At this writing, although full clarification has not yet occurred, it appears that appropriate relief will be found in the "routine use" provisions of the Act, under which uses not inappropriate to the purpose for which the information was originally collected, may continue if declared to be "routine" by the agency possessing the file, and so published in the Federal Register. Requests for such publication have been made to the three armed services and to the Veterans Administration and it is expected that the Agency's privilege of using the records will be preserved by this provision.

Medical genetic studies of veteran twins (National Institutes of Health)

A panel of 15,900 pairs of twin veterans has been established with support from the Veterans' Administration and from the National Institutes of Health to make possible the conduct of epidemiologic and medical genetic studies. The panel became accessible to investigators in 1967. Since that time a number of studies have been completed and reports have been published.

Using questionnaires and clinical examinations it has been possible to control genetic influences in evaluations of the commonly recognized risk factors of coronary heart disease and of chronic obstructive pulmonary disease. A study of changes in ocular pressure following topical administration of corticosteroids indicated that this phenomenon is not based on a simple genetic mechanism as had been believed previously. The influence of genetics in schizophrenia and in effective psychosis has been assessed relative to psychoneurosis. An evaluation was made of the importance of heredity in several diseases including selected dermatologic disorders, multiple sclerosis, and headache and in diagnostic indices such as the Type A behavior pattern defined by Friedman and Rosenman, the scales of the California Psychological Inventory, and the serum levels of Immunoglobulin E. Mechanisms of deposition of particles in lungs and their subsequent clearance have been studied to evaluate the significance of genetics in these processes.

A current extensive undertaking is a study of the quantitative effects of schooling, innate abilities, and family structure on earnings. To collect the necessary data, a large questionnaire mailing was made to members of the panel. The study is being extended to include career information from military service records. Through the questionnaire

it has been possible to determine the contribution of heredity to income and education. The study of military records will make it possible to study native ability and also to evaluate the extent to which interrelationships of these three variables are influenced by heredity.

Ascertainment of mortality in the panel through the record system of the Veterans' Administration makes it possible to monitor deaths due to different causes in the twin panel. Such investigations are under way with respect to coronary heart disease, cancer, and other clinical entities. The group has now reached an age where a significant number of deaths from medical causes occurs each year and continued monitoring of mortality in this group promises to provide valuable information regarding the relative importance of genetic factors in chronic and other diseases.

Epidemiologic study of multiple sclerosis in U.S. military veteran population (National Institute of Neurological and Communicative Disorders and Stroke)

This study of the epidemiology of multiple sclerosis has two basic objectives: (1) to determine, if possible, by focusing attention on a group of cases with place of birth and place of induction into the military in different sections of the country (migrants), whether circumstances producing the disease occur closer to birth than to entry into service, and (2) to investigate further, achieving more precision through the use of large samples of cases and controls, the relative importance of the preservice characteristics identified in earlier studies as factors distinguishing cases and controls: urbanization, socioeconomic status, race, and visual acuity. Also being examined is the question whether these factors are equally important among females, and whether there is interaction between race and other factors. The study of migrants is based upon the known variation with latitude of the risk of MS. By drawing upon the several thousand veterans of World War II and of the Korean War who were granted compensation for MS, a series of 5,300 case-control pairs has been assembled, approximately 10 percent of whom have been identified as migrants. Included among these cases is a series of some 175 black males and about 185 females. Controls have been selected from a roster of National Service Life Insurance policyholders during World War II and a 0.1 percent sample of all servicemen during the 1950–70 period, and have been matched to cases on the basis of age, branch of service, and date of entry.

White male cases and controls number about 4,400 in each group. Among these men, case-control ratios for non-migrants of the northern, middle, and southern tiers, respectively, are 1.38, 0.97, and 0.54. In every case, the ratios for migrants fall between those for the tiers of birth and induction.

Socioeconomic status and visual acuity have been confirmed as associated factors of risk for the disease among white males in this larger sample. No case/control differences have been found in the preservice incidence of childhood communicable diseases.

States of induction bearing the highest risk for MS all lie north of 39° latitude. Specific counties with the highest risks, whether as residences of birth or induction, lie north of 44° latitude and are

located in the states of Washington, Minnesota, and Maine. A report summarizing these and other findings will be forthcoming.

Epidemiologic and follow-up study of amyotrophic lateral sclerosis and other motor neuron disease (National Institute of Neurological and Communicative Disorders and Stroke)

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease of unknown etiology, rapidly fatal course, and very low incidence, about one per 100,000 population per year. A three-part study of the epidemiology and natural history of ALS and other possibly related motor neuron diseases is in progress. Its purpose is to seek factors associated with ALS and to attempt some clarification of the essential similarities and differences with these other diseases.

Parts 1 and 2 are epidemiologic studies; Part 3 is a natural history study. In Part 1, a World War II service record investigation of 500 veterans of the period who died of ALS during the years 1963–67 is being made, comparing these men with controls matched for age, branch, and date of entry into service. Data collection and coding of this phase is essentially complete.

The final interview sample of Part 2, designed to elicit more extensive and detailed information from ALS patients and controls hospitalized in the VA system, numbers slightly more than 130 cases and half as many controls (malignant brain tumor patients).

A roster of some 2,600 patients discharged from Veterans' Administration hospitals during 1957–69 with a diagnosis of ALS has been created from two tape files provided by the Veterans' Administration. The results of a pilot sample indicate that 750 individuals should be selected from this roster in order to realize a sample of 500 patients for whom the necessary data on signs and symptoms at onset and diagnosis can be obtained for the prognostic study of Part 3.

Analysis of these samples will probably begin in late 1975.

Epidemiology of Hodgkin's disease (National Cancer Institute)

Hodgkin's disease, as suggested by recent epidemiological studies, is probably two or three distinct entities, one of which has onset characteristically between ages 20 and 30. Evidence has also shown that, for the disease of early adult life, the risk varies with a number of demographic and environmental characteristics, posing an infectious etiology as a serious possibility. This study is exploiting the large U.S. military experience to investigate the disease in a population of young adult males which is relatively unbiased by social and geographic origins and by prior medical history. About 650 men under 31 years of age and with at least one year of duty prior to diagnosis in a military hospital, in the period 1950–68, have been matched with controls on the basis of branch, year of birth, and service entry date.

This project is now in the analysis phase. Findings thus far continue to support the hypothesis of an infectious agent, possibly a "slow virus." A strong inverse relationship between the risk of the disease and sibship size has been found. In addition, an urban induction residence (especially the northeastern U.S.), tonsillectomy prior to induction, and a high score on the military general aptitude test increase the risk of Hodgkin's disease. The remaining analysis includes a search for space-time clusters of the cases and an analysis of much of

the data *within* each of the four major pathologic types of the disease obtained from a current examination and reclassification of tissue specimens.

Causes of death following occupational exposure to microwave radiation (RADAR) (Bureau of Radiological Health)

A population-based prospective study has been planned in collaboration with an investigator at the Bureau of Radiological Health. The investigation will make use of occupational differences in levels of shipboard exposure to microwave radiation of Navy personnel during the Korean War period. Two groups of approximately 20,000 men each, one maximally exposed and the other minimally exposed, will be compared with respect to (1) mortality, with attention to specific diagnosis, (2) hospitalized illness at the time of occupational exposure, and (3) later disability. The period of ascertainment will be 1950–1974 for mortality, 1950 through 1960 for Navy hospitalization, and 1963–1974 for hospitalization in Veterans Administration facilities.

Rosters of cases and controls have been built from records of graduating classes of Navy Class A schools. Men graduating as either Electronics Technicians or Fire Control Technicians were assigned to the maximally exposed cohort, while Radio Operators and Radar Operators comprise the control cohort.

Mortality has been ascertained, with some 1,400 deaths reported. The cause of death has been determined for about two-thirds of these and coding of causes will begin soon.

Cancer mortality among World War II X-ray technicians (Bureau of Radiological Health)

An earlier study by the Medical Follow-up Agency of 6,500 men who were trained as X–ray technicians in the Army during World War II and a comparably-sized group of controls (pharmacy technicians and medical laboratory technicians) revealed that, during the period 1946–1963, the former X-ray technicians had no abnormal mortality patterns for any disease that could be associated with X-ray exposure.

In recent years, it has become clear that ionizing radiation is a potent carcinogen and that the latent period for induction of solid tumors, especially, may be several decades. The Bureau of Radiological Health, therefore, has asked the Medical Follow-up Agency to examine the more recent mortality patterns in the group included in the earlier study to determine whether any X-ray effect had become discernible in the period 1964–1974. The rosters have been checked against BIRLS, and death certificates are now being collected and coded as to cause of death. The study will be completed during fiscal year 1976.

Epidemiology of childhood cancer, with reference to prenatal X-ray (National Cancer Institute)

Several investigations, with conflicting results, have been made of the hypothesis that X-ray doses on the order of one to two rads, received by fetuses while their mothers were having abdominal X-rays, resulted in a significantly increased risk of cancer before the age of 10. Some of the results of previous studies may have been influenced by social class differences between mothers who were X-rayed and

those who were not. It was decided, therefore, to study the question among births in military hospitals, where the decision whether or not to X-ray the prospective mother would be unaffected by her ability to pay, but would be determined almost exclusively by medical considerations.

Name, date of birth, and other identifying information were obtained from the National Cancer Institute for each of the approximately 39,000 children under 18 years of age who died of cancer in the United States during the years 1960–1969. The name of the hospital in which birth occurred was obtained primarily from the state of birth, but in rare instances from hospitals themselves.

About 1,400 births occurring in military hospitals were thus identified and the clinical records for slightly over 1,000 of these were located in the files of the National Personnel Records Center in St. Louis, Missouri.

Records abstracting for all cases and twice as many controls has been completed and the file is being readied for analysis.

Follow-up studies of World War II veterans with certain conditions possibly related to cancer (National Cancer Institute)

Groups of World War II veterans thought to be at differential risk for some forms of cancer, as a result of some medical condition or operation experienced while in service, have been assembled from the hospital admissions files of the Army in 1944 and 1945.

Two broad groups of studies are in progress. The first, related to abnormalities in immunological competence while in service, is composed of men having allergies or splenectomy. The other group consists of men with any orchidopexy, nephrectomy, or chronic alcoholism.

This investigation, being done in collaboration with members of the Epidemiology Branch of the National Cancer Institute, will ascertain and analyze mortality of these men and their matched controls to determine if an excess of mortality from cancer or other causes of death exists.

Probing studies of this type have recently become more feasible because the mechanism now exists for relatively inexpensive records linkage between the Veterans' Administration files and the military hospital admission files, both of which have been computerized. All investigations in studies of this nature have a common procedural link in that the initial condition is verified from the hospital admissions file, and the fact, as well as the certified cause in most instances, of mortality is obtained from the Veterans Administration.

Approximately 34,000 men have been selected for the study. Mortality ascertainment has been completed, with approximately 7,300 deaths having been identified. Information on cause of death has been obtained for some 80 percent of the deaths and coding of cause of death has begun.

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